Susceptibility to SARS-CoV-2 infection in patients undergoing chemotherapy and radiation therapy

Claudia Rita Corso [a,b], Natalia Mulinari Turin de Oliveira [a,b], Daniele Maria-Ferreira [a,b,*]

[a] Instituto de Pesquisa Pelé Pequeno Príncipe, Faculdades Pequeno Príncipe, Curitiba, Paraná, Brazil
[b] Programa de Pós-graduação em Biotecnologia Aplicada à Saúde da Criança e do Adolescente, Faculdades Pequeno Príncipe, Curitiba, Paraná, Brazil

ARTICLE INFO

ABSTRACT

The outbreak of the new coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly become a public health emergency of international concern, especially affecting the elderly people and patients with chronic disease, such as hypertension and respiratory syndromes. Patients undergoing chemotherapy treatment (e.g., bleomycin, cyclophosphamide, methotrexate, monoclonal antibodies, and paclitaxel therapy) are vulnerable to the development of respiratory syndromes induced by chemotherapeutic agents and are also more susceptible to viral infections as they are immunosuppressed. Neutropenia is an important risk factor for increased vulnerability to infections, as a respiratory syndrome involves an array of immune cells maintaining the balance between pathogen clearance and immunopathology. However, the differential diagnosis of pulmonary symptoms in cancer patients is broad, with complications being related to the malignancy itself, treatment toxicity, and infections. The risk factors depend on the specific type of cancer, chemotherapy, patient characteristics, and comorbidities. Thus, this review discusses the main events implicated in immunosuppression caused by chemotherapy and radiation therapy and the association of immunosuppression and other factors with SARS-CoV-2 infection susceptibility in cancer patients; and, importantly, how to deal with this situation in face of the current pandemic scenario.

Contents

* Corresponding author at: Instituto de Pesquisa Pelé Pequeno Príncipe, Av. Silva Jardim, no 1632, Água Verde, Curitiba, Paraná 80250-060, Brazil.
E-mail address: daniele.ferreira@pelepequenoprincipe.org.br (D. Maria-Ferreira).

SARS-CoV-2 infection

The outbreak of coronavirus disease (COVID-19), caused by a novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in the Hubei Province, China. Since then, COVID-19 has rapidly spread around the world. The increasing number of cases and deaths worldwide has forced many countries to go into lockdown in an attempt to contain the spread of the virus. As of August 10th, 2020, more than twenty million confirmed cases of the disease have been globally recorded, with nearly 700 thousand deaths. Owing to the markedly high transmission capacity, the World Health Organization declared COVID-19 a public health emergency of international concern, and every country implemented community mitigation strategies to slow the spread of the pandemic.

The disease caused by SARS-CoV-2 is pathogenically similar to that caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [1]. A phylogenetic analysis of the coronavirus genomes indicated that SARS-CoV-2, SARS-CoV, and MERS-CoV, were all members of the β-coronavirus genus and were included in the β-coronavirus 2b lineage, which includes viruses that generally infect the mammals and humans [2].

The viral attachment to the host's cell membrane is a critical initial step. A homotrimer spike glycoprotein on the virus surface mediates the coronavirus entry by binding to the metallopeptidase angiotensin-converting enzyme 2 (ACE2) receptors [3] which are expressed in the kidney, heart, blood vessels, gastrointestinal tract cells, and alveolar epithelial cells, which are particularly susceptible to viral infection [4]. Additionally, ACE2 was previously recognized as the functional receptor for SARS-CoV. Besides, atomic-level structural information has shown that SARS-CoV and SARS-CoV-2 display similar spikes and receptor binding domain sequences [5].

COVID-19 spreads by direct contact, respiratory secretion, and droplets. The rapid and persistent viral replication contributes to cellular apoptosis and subsequent cytokine storm [6]. Patients with severe COVID-19 generally have a hyperactivated inflammatory status, with increased interleukin 1β (IL-1β), IL-4, IL-6, interferon γ (IFN-γ) and interferon-inducible protein 10 (IP-10) levels, for example, associated with interstitial pneumonia, alveolar damage, and respiratory failure [7]. Indeed, studies on host immune responses to COVID-19 shown that approximately 80% of the patients develop peripheral blood lymphopenia, which suggests cellular infiltration and lung injury through apoptosis [8]. By analyzing the cytometric data, a study reported that patients with COVID-19 showed decreased CD4/CD8 levels in addition to increased CCR6+ Th17 cell counts among the CD4 + T cells and lymphocyte lung infiltration [9]. However, the disease progression, as well as the cellular ratios, can change depending on the infection complexity. Nonetheless, evidence regarding infection susceptibility and disease development is growing.

So far, it appears that intrinsic host factors may influence a patient's susceptibility to COVID-19 [10]. For example, older people, those with comorbidities, such as hypertension and diabetes, and cancer patients undergoing chemotherapy and radiotherapy, may rapidly develop acute respiratory distress syndrome and have a higher risk of death [11]. On the other hand, many have concentrated on examining the role of genetic predisposition, such as differences in leukocyte antigen genes and blood type, or the expression levels of tissue proteins, among others, as factors resulting in higher SARS-CoV-2 infection susceptibility, and a worse disease outcome [12]. However, further research is still required.

From this standpoint, several factors typically increase infection risk in patients receiving cytotoxic chemotherapy and radiotherapy due to immune system impairment. In general, cancer patients are more vulnerable to COVID-19 [13]. Furthermore, the rapid disease spread and reduced ability to receive hospital and/or medical services required due to the outbreak may be concerning for patients with cancer. Considering the factors above, and to better understand the impact of COVID-19 in patients with cancer, the mechanisms involved in immunosuppression caused by chemotherapy and radiation therapy, and its relationship to SARS-CoV-2 infection susceptibility will be discussed.

Chemotherapy and radiotherapy-induced immunosuppression and lung injury

Cancer is a significant public health issue worldwide, with an estimated 18.1 million new cancer cases in 2018. Lung cancer is one of the most common malignancies in both males and females and is associated with a high death rate [14]. In general, the therapy strategy includes chemotherapy, radiation, and surgery when appropriate. The development of the first chemotherapy agent in 1940, nitrogen mustards [15], improved the cancer treatment protocols regarding tumor development, metastasis, cancer relapse, and overall mortality. Since then, positive impacts on lifespan, quality of life, and life expectancy of cancer patients have been reported [16]. However, many classes of chemotherapies and ionizing radiations have a number of adverse side effects, including significant acute and/or chronic lung injuries such as acute bronchoconstriction, interstitial pneumonitis, pulmonary veno-occlusive disease, pulmonary hypertension, bronchiolitis obliterans, organizing pneumonia, intra alveolar fibrosis, and respiratory failure. Herein, we will discuss the mechanism under chemotherapy- and radiotherapy-induced immunosuppression and lung injury.

Chemotherapy

Chemotherapeutic drugs reported to induce pulmonary toxicity include: (i) antitumor antibiotics; (ii) alkylating agents; (iii) platinoids; (iv) antimetabolites; (v) nitrosoureas; (vi) receptor tyrosine kinase inhibitor; (vii) topoisomerase inhibitor; (viii) proteasome inhibitor; (ix) mTOR inhibitors; (x) taxanes; (xi) monoclonal antibodies and (xii) immune checkpoint inhibitors [16].

The main mechanism involved in pulmonary morbidities induced by chemotherapy comprises the induction of DNA damage, inflammation, oxidative stress, senescence, and cell death. This leads to an impaired physiological condition with subsequent lung injury [17]. Some studies have reported the involvement of tumor necrosis factor-α (TNF-α), IL-1β, IL-6 and IL-23, T-lymphocytes, macrophages, neutrophils, and eosinophil infiltration in alveoli inflammation (alveolitis), in addition to an over-proliferation of fibroblasts and excess collagen deposition [18,19]. Fibrosis development has been associated with an increase in transforming growth factor-β (TGF-β) release due to a sustained pulmonary inflammatory environment attributed mainly to IL-1β [20].

Additionally, the pulmonary toxicity of the immune checkpoint inhibitors (PD-1 inhibitors: Pembrolizumab and Nivolumab) and anti-CTLA-4, are related to an overstimulation of the immune system on the effector T cells and release of cytokines in the lung in up to 9% of patients [21]. Nevertheless, even after treatment discontinuation, the risk of pneumonitis extends for up to 24 months [21,22]. Overall, pneumonitis incidence may be potentially higher when the therapeutic strategy includes drug association.

Pneumonitis and fibrosis are the main representative conditions induced by bleomycin, an antitumor antibiotic. Notably, up to 10% of the patients develop the clinical pulmonary disease, with a mortality rate of nearly 20% [23]. Patients may also develop organizing pneumonia and interstitial lung disease, which is clinically manifested by fever, dry cough, and dyspnea [24].

Immunological and non-immunological factors are mechanistically involved in taxane-induced pulmonary toxicity. The impairment of the helper/suppressor T cell ratio in paclitaxel monotherapy and depletion of CD4$^+$ T, CD8$^+$ T, natural killer cells, and B cells on the administration of paclitaxel in combination with radiation can result in susceptibility to infection and pneumonia [25,26]. These alterations create the basis for the establishment and progression of opportunistic infections and interstitial pneumonia [26]. Paclitaxel also increases the alveolar capillary membrane permeability, thus, resulting in several adverse effects, including pulmonary diffusion dysfunction [27].

Myelosuppression can also occur in patients with cancer who are undergoing chemotherapy. These drugs are cytotoxic to tumor cells but often affect the healthy cells under mitosis, including the bone marrow cells, which are mitotically active [28]. Decreased neutrophil counts are often accompanied by decreased hematopoietic cell counts (hemoglobin level and platelet count) [29]. Immunoglobulin production and the T lymphocytes, monocytes/macrophages, and complement cascade are also negatively affected by chemotherapy treatment with almost all classes of anti-cancer drugs [30]. During immune suppression, type 2 macrophages, IL-1, IL-10, TGF-β, and PGE$_2$ are significantly involved in the local and systemic suppression of the Th1 and Th2 responses, and, consequently in bacterial, viral, and fungal infections [30].

Radiotherapy

The lung is a radiosensitive organ, thus radiation induce-pneumonitis and -pulmonary fibrosis are the most common pulmonary side effects in radiotherapy. Pneumonitis, which is characterized by extensive lung inflammation, is the most common pulmonary toxicity and affects up to 15% of the irradiated patients with high doses soon after the termination of treatment. Moreover, pneumonitis progresses to lung fibrosis in some patients. Many factors influence the pulmonary toxicities induced by radiotherapy, such as the volume of lung irradiated, in cases of lung cancer; dose regimen; and radiation therapy combined with chemotherapy [31]. Patients exposed to radiation may develop pneumonitis within 2–4 months of treatment [32].

The damage induced by radiation to the epithelial cells induces the production of oxygen reactive species and DNA damage [33]. This event triggers an early immune response by the secretion of pro-inflammatory cytokines, such as IL-1 and TNF-α, through activation of the nuclear factor kappa-B (NF-κB) signaling pathway [34]. This molecular cascade recruits immune cells such as lymphocytes, which were involved in early lung inflammation [33]. If lung injury persists, it evolves to lung fibrosis. The regulatory t cells (Treg) play an essential role in the modulation of pulmonary fibrosis induced by radiation. Treg promotes the accumulation of fibrocyte; β-catenin-mediated epithelial-mesenchymal transition; shift Th1/Th2 cytokine balance, increasing the secretion of pro-fibrotic cytokines; and suppress Th17 response [31]. Besides, radiation therapy also stimulates the secretion of TGF-β, which contributes to the development of lung fibrosis [32].

The clinical management of patients suspected of having pulmonary disease related to chemotherapeutic drug or ionizing radiation use involves dose reduction, treatment delay, and drug withdrawal or drug substitution to avoid permanent complications [16]. Ideally, the patient's cancer stage and type must be considered in therapeutic decision-making. As the host's defense mechanisms of patients under chemotherapy and radiotherapy are already compromised by the malignancy itself, an infection, together with pulmonary toxicity, may be potentially critical and affect the course of treatment, tumor progression, and patient survival. Accordingly, this is now to be discussed.

SARS-CoV-2 infection in patients undergoing chemotherapy and radiotherapy

As highlighted previously, patients with cancer who are undergoing chemotherapy and/or ionizing radiation are more susceptible to SARS-CoV-2 infection because of their immunosuppressive state. Consequently, this specific subgroup might be at increased risk of disease development and poorer prognosis. At present, the cancer community has gained knowledge, but still, has several concerns essentially due to the potential overlap in the number of cases admitted to hospitals and treatment prioritization.

In patients with cancer, the lung inflammatory process can be worse due to alveolar-capillary disruption caused by some chemotherapy drugs [27]. Alveolar disturbance facilitates the virus entry through the ACE2 receptors. This process increases cell infiltration (e.g., neutrophils and eosinophils), leading to inflammation of the lungs through cytokine release; and induces pneumonia and alveolar damage in some cases. Considering this, the synergism hypothesis between this condition and the exaggerated release of pulmonary cytokines in COVID-19 cannot be excluded (Fig. 1). The differential diagnosis of pulmonary disease in patients with cancer may be broad and include aspects related to the malignancy itself, treatment toxicities, or infections. The white blood cell alterations, including increased neutrophils and eosinophils levels and clinical symptoms (cough, fever, dyspnea, and chest discomfort) are nonspecific and can be observed in both COVID-19 and pulmonary toxicity induced by chemotherapy [7,18,19]. In most cases, the toxicity induced by chemotherapy occurs within the first few weeks or months, whereas in COVID-19, it occurs in days. Notable exceptions include bleomycin, busulfan, and nitrosoureas, which may induce pulmonary fibrosis over an extended period [30,35]. Together with COVID-19, lung injury, and myelosuppression induced by chemotherapy treatment and/or weakness of the immune system due to cancer progression, are linked to a poorer prognosis.

In China, it was observed that patients with cancer had a higher risk of COVID-19 infection than individuals without cancer [36,37]. This was associated with a history of chemotherapy or surgery in the month preceding the infection [36]. Zhang et al. [38] described the deteriorating condition and poor outcomes of 28 cancer patients with severe COVID-19. Patients undergoing chemotherapy had an increased risk of developing severe symptoms, after 14 days of being diagnosed with COVID-19 [38]. Despite the small number of patients in these studies, the evidence already suggests a high susceptibility of cancer patients, particularly those with lung cancer, to COVID-19 development.

A study conducted in the Royal Marsden Hospital (London, UK), also indicated that the use of systemic anticancer therapy appears to be associated with a modest risk of severe COVID-19 [39]. Of the 101 patients admitted to the hospital and included in the study, 29 (28%) died due to COVID-19. The patients had site-specific diagnoses of hematological (37%), gastrointestinal (20%), thoracic (13%), urological (13%), breast (6%), gynecological (3%), and central nervous system (3%) malignancies. The patients presented infiltrates on chest imaging, had a lower lymphocyte and platelet count, besides higher levels of C-reactive protein. Importantly, the mortality was associated with the presence of inflammatory infiltrates on chest imaging and with a lower platelet count [39].

An association between the degree of inflammation resulting from SARS-CoV-2 infection and disease severity has been observed in three cases of cancer patients in Wuhan, China. A reduction in all lymphocyte subsets (CD3$^+$CD4$^+$ helper T cells, CD3$^+$CD8$^+$ cytolytic T and B cells, and NK cells) was observed. The cell count profile for CD3$^+$ CD4$^+$ helper T cells was significantly lower in two severe COVID-19 cases when compared to the common and mild COVID-19 cases [40]. Lower lymphocyte counts were also observed during
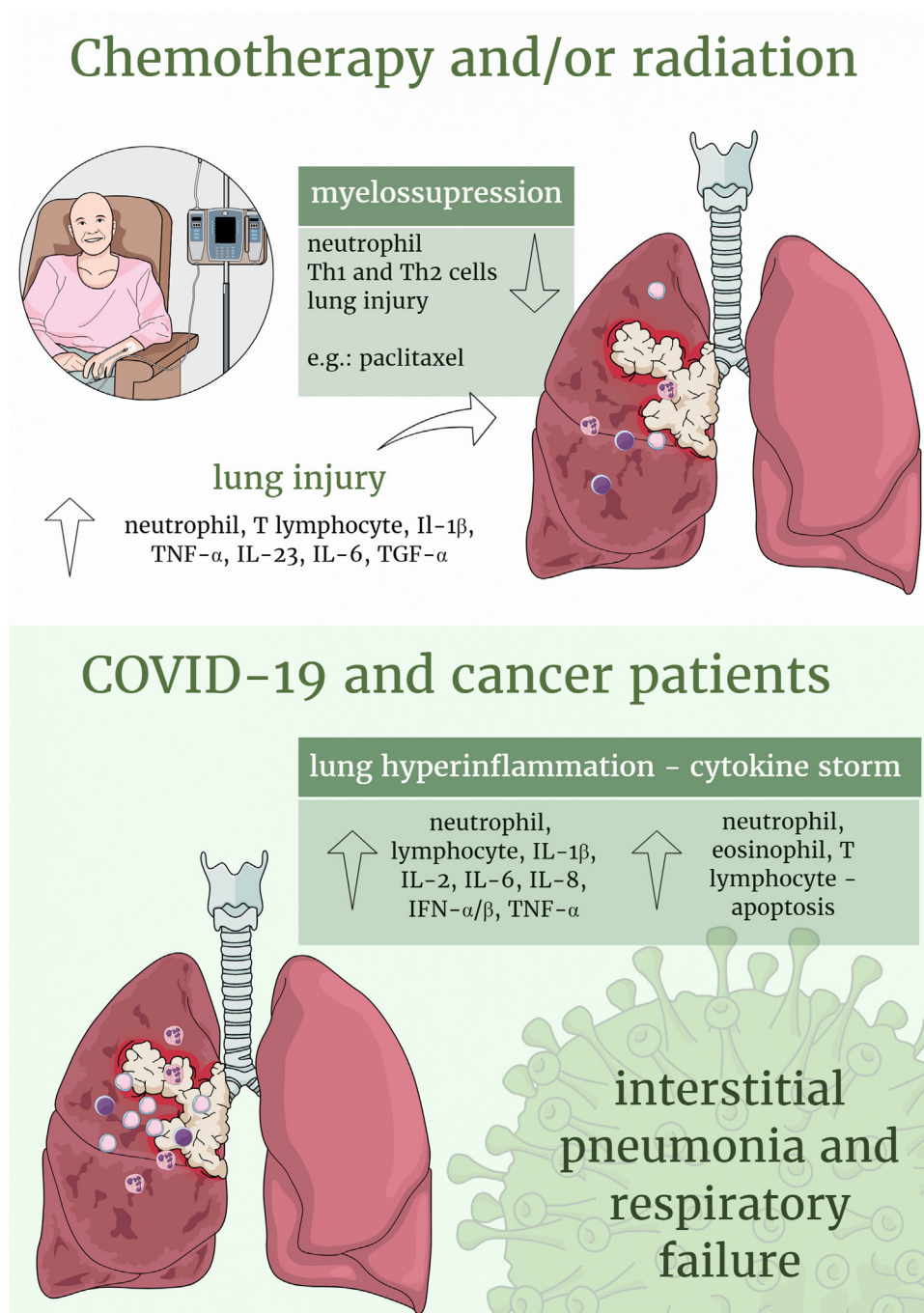
Fig. 1. Schematic showing the SARS-CoV-2 infection susceptibility in patients undergoing chemotherapy and/or radiation therapy. Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Disease transmission primarily occurs through direct contact, respiratory secretion, and droplets. The main symptoms include dry cough, headache, fatigue, fever, dyspnea, and alveolar damage, as well as respiratory syndrome in severe cases. Patients undergoing chemotherapy (e.g., paclitaxel) and radiotherapy are more susceptible to infection due to immunological impairment and alveolar disturbance caused by these drugs. These impairments facilitate virus entry, and an excessive inflammatory response is initiated (e.g., increased neutrophil and eosinophil infiltration), contributing to the worsening of lung damage.

SARS-CoV infection in 2003 and related to disease severity [41,42]. The reduction of peripheral lymphocytes, including CD3^{+}, CD4[+,] and CD8^{+} T cells, was strongly associated with COVID-19 severity and outcome [43,44], whilst T cells reduction was related to the infiltration and sequestration of lymphocytes in lungs and other affected organs, leading to cytokine secretion and disease aggravation [41,42].

Despite the limited number of cancer patients, the data available has raised a highly important debate on the importance of cancer drugs and the immunosuppressive state as influencing factors of disease outcome in this specific population. Thus far, clinicians have gained experience during the pandemic, but data are still emerging. Adding to the complexity of this scenario, other factors, such as non-cancer comorbidities, also play a role during SARS-CoV-2 infection.

The mortality rate among cancer patients with COVID-19 appears to be related not only to anticancer therapy but also to age and multiple preexisting non-cancer comorbidities [45]. Of importance, a prospective cohort study showed that 800 patients with active cancer and symptomatic SARS-CoV-2 infection, presented non-cancer comorbidities, including hypertension (31%) – the great

majority; diabetes (16%), cardiovascular diseases (14%), and chronic obstructive pulmonary disease (8%) [36,45].

In this context, comprehensive medical support should be provided for patients with cancer who are diagnosed with COVID-19, particularly those that are elderly or have comorbidities [46]. The decision to discontinue chemotherapy and/or radiotherapy should be carefully made after other causes are excluded, such as other infections or cancer progression. If a patient with the acute pulmonary syndrome is infected by SARS-CoV-2, diagnostics should be rapidly performed, and a ventilator must be sourced. If initially, drug-related pulmonary toxicity is considered a symptom, the adverse effects of chemotherapy may progress.

Treatment prioritization

The official French guideline suggests that patients with cancer and COVID-19 should discontinue systemic anticancer treatment until the complete resolution of their symptoms [37]. Landman et al. [46] also proposed postponing adjuvant chemotherapy or elective surgery for patients with stable cancer. Despite the limitations of the study, Zhang et al. [47] reported that those on active anticancer therapy (chemotherapy, radiotherapy, targeted therapy, and immunotherapy combined with chemotherapy), within 14 days before COVID-19 diagnosis experienced severe events, clearly showing the vulnerability of cancer patients in the current pandemic scenario. The evidence has raised an important debate on whether cancer treatment should be discontinued or if targeted treatment should be maintained in patients with cancer who are diagnosed with COVID-19 [48]. Of course, additional care must be considered for aggressive cancers, and the risk-benefit of cancer treatment should be precisely discussed. Additional studies are required so that a consensus can be reached.

Future perspectives

Cancer patients are at increased risk of COVID-19 serious events because of their immunocompromised state in comparison to the general population. Therefore, particular attention should be given to patients undergoing chemotherapy and radiation. As there is no universal oncological consensus, and it is hard to predict the resolution of the COVID-19 pandemic, identifying the mechanism of action of employed drugs during cancer treatment, and the possible adverse effects is crucial. Those with specific comorbidities that are considered as risk factors of more severe COVID-19 should be identified by oncologists at an early stage as potentially having a poor prognosis. Limited access to hospitals and proper isolation protocols for cancer patients should be considered to mitigate the risk of COVID-19. Considering these, oncology societies around the world have developed guidelines to avoid the negative effects of the COVID-19 pandemic on the management of cancer patients. A conceptual framework for prioritizing the use of radiotherapy and systemic treatments during the pandemic was proposed. If alternative and palliative treatments exist or if a delay is not expected to affect the outcomes, patients should be given a lower priority. However, if an imminent risk of early mortality, potential high morbidity, impaired quality of life, or definitive curative treatments exist, patients should be given a higher priority for continuing treatment [49]. Thus, to limit viral transmission during the COVID-19 outbreak, meticulous and individualized clinical management of patients with cancer should be done to protect them in a way that has the least impact on their cancer treatment and quality of life. Some strategies may also be adopted by hospitals, including the development of a COVID-19 policy for cancer care, reduce clinic visits, remote care, and use of existing digital health platforms,

amongst others, to ensure that cancer patient care is not completely discontinued during the pandemic [50].

COVID-19 management in the oncology context is not an easy task. Data on the subject are still insufficient as it continues to be collected from hospitals all around the world with the ongoing pandemic. By comprehending which is the best option for the management of cancer patients, it will be easier to direct rules to avoid disease contagion and progression and to be more prepared to handle future pandemics.

Author contributions statement

DM-F, CRC, and NMTdO contributed to the conception and design, drafted, and critically revised the manuscript. All authors have approved it for publication.

Competing interests

None declared.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2021.03.008.

References

[1] Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020;7:11, http://dx.doi.org/10.1186/s40779-020-00240-0.

[2] Yang P, Wang X. COVID-19: a new challenge for human beings. Cell Mol Immunol 2020;17:555–7, http://dx.doi.org/10.1038/s41423-020-0407-x.

[3] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;17:94–7, http://dx.doi.org/10.1128/jvi.00127-20.

[4] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21, http://dx.doi.org/10.1016/S2213-2600(20)30116-8.

[5] Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 2020;581:215–20, http://dx.doi.org/10.1038/s41586-020-2180-5.

[6] Yang Y, Shen C, Li J, Yuan J, Yang M, Wang F, et al. Exuberant elevation of IP-10, MCP-3 and IL-1RA during SARS-CoV-2 infection is associated with disease severity and fatal outcome. MedRxiv 2020, http://dx.doi.org/10.1101/2020.03.02.20029975.

[7] Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med 2020;26:453–5, http://dx.doi.org/10.1038/s41591-020-0819-2.

[8] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20, http://dx.doi.org/10.1056/nejmoa2002032.

[9] Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. Immunotherapy 2020;12:269–73, http://dx.doi.org/10.2217/imt-2020-0067.

[10] Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care 2020;24:108, http://dx.doi.org/10.1186/s13054-020-2833-7.

[11] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109, http://dx.doi.org/10.1016/j.jaut.2020.102433.

[12] Zhao J, Yang Y, Huang H-P, Li D, Gu D-F, Lu X-F, et al. Relationship between the ABO blood group and the COVID 19 susceptibility. MedRxiv 2020, http://dx.doi.org/10.1101/2020.03.11.20031096.

[13] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424, http://dx.doi.org/10.3322/caac.21492.

[14] Smith SL. War! What is it good for? Mustard gas medicine. CMAJ 2017;189:E321–2, http://dx.doi.org/10.1503/cmaj.161032.

[15] Li L, Mok H, Jhaveri P, Bonnen MD, Sikora AG, Eissa NT, et al. Anticancer therapy and lung injury: molecular mechanisms. Expert Rev Anticancer Ther 2018;18:1041–57, http://dx.doi.org/10.1080/14737140.2018.1500180.

[16] Hecht SM. Bleomycin: New perspectives on the mechanism of action. J Nat Prod 2000;63:158–68, http://dx.doi.org/10.1021/np990549f.

[17] Piguet PF, Collart MA, Grau GE, Kapanci Y, Vassalli P. Tumor necrosis factor/cachectin plays a key role in bleomycin-induced pneumopathy and fibrosis. J Exp Med 1989;170:655–63, http://dx.doi.org/10.1084/jem.170.3.655.

[18] Ekstrand-Hammarström B, Wigenstam E, Bucht A. Inhalation of alkylating mustard causes long-term T cell-dependent inflammation in airways and growth of connective tissue. Toxicology 2011;280:88–97, http://dx.doi.org/10.1016/j.tox.2010.11.012.

[19] Kolb M, Margetts PJ, Anthony DC, Pitossi F, Gauldie J. Transient expression of IL-1β induces acute lung injury and chronic repair leading to pulmonary fibrosis. J Clin Invest 2001;107:1529–36, http://dx.doi.org/10.1172/JCI12568.

[20] Simpson AB, Paul J, Graham J, Kaye SB. Fatal bleomycin pulmonary toxicity in the west of Scotland 1991-95: a review of patients with germ cell tumours. Br J Cancer 1998;78:1061–6, http://dx.doi.org/10.1038/bjc.1998.628.

[21] Abdel-Rahman O, Elhalawani H, Fouad M. Risk of elevated transaminases in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Expert Opin Drug Saf 2015;14:1507–18, http://dx.doi.org/10.1517/14740338.2015.1085969.

[22] Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ 2014;21:15–25, http://dx.doi.org/10.1038/cdd.2013.67.

[23] Watson RA, De La Peña H, Tsakok MT, Joseph J, Stoneham S, Shamash J, et al. Development of a best practice clinical guideline for the use of bleomycin in the treatment of germ cell tumours in the UK. Br J Cancer 2018;119:1044–51, http://dx.doi.org/10.1038/s41416-0180300-x.

[24] Reckzeh B, Merte H, Pflüger KH, Pfab R, Wolf M, Havemann K. Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small-cell lung cancer. J Clin Oncol 1996;14:1071–6, http://dx.doi.org/10.1200/JCO.1996.14.4.1071.

[25] Fujimori K, Yokoyama A, Kurita Y, Uno K, Saijo N. Paclitaxel-induced cell mediated hypersensitivity pneumonitis. Diagnosis using leukocyte migration test, bronchoalveolar lavage and transbronchial lung biopsy. Oncology 1998;55:340–4, http://dx.doi.org/10.1159/000011873.

[26] Liu WJ, Zhong ZJ, Cao LH, Li HT, Zhang TH, Lin WQ. Paclitaxel-induced lung injury and its amelioration by parecoxib sodium. Sci Rep 2015;5:12977, http://dx.doi.org/10.1038/srep12977.

[27] Nishino M, Sholl LM, Hodi FS. Anti-PD-1-related pneumonitis during cancer immunotherapy. N Engl J Med 2015;373:288–90, http://dx.doi.org/10.1056/NEJMc1505197.

[28] Kasi PM, Grothey A. Chemotherapy-induced neutropenia as a prognostic and predictive marker of outcomes in solid-tumor patients. Drugs 2018;78:737–45, http://dx.doi.org/10.1007/s40265-018-0909-3.

[29] Vento S, Cainelli F. Infections in patients with cancer undergoing chemotherapy: aetiology, prevention, and treatment. Lancet Oncol 2003;4:595–604, http://dx.doi.org/10.1016/S1470-2045(03)01218-X.

[30] Reinert T, da R. Baldotto CS, Nunes FAP, de S. Scheliga AA. Bleomycin-induced lung injury. J Cancer Res 2013;2013:1–9, http://dx.doi.org/10.1155/2013/480608.

[31] Guo T, Zou L, Ni J, Zhou Y, Ye L, Yang X, et al. Regulatory T cells: an emerging player in radiation-induced lung injury. Front Immunol 2020;11:1769, http://dx.doi.org/10.3389/fimmu.2020.01769.

[32] Kainthola A, Haritwal T, Tiwari M, Gupta N, Parvez S, Tiwari M, et al. Immunological aspect of radiation-induced pneumonitis, current treatment strategies, and future prospects. Front Immunol 2017;8:506, http://dx.doi.org/10.3389/fimmu.2017.00506.

[33] Wirsdörfer F, Jendrossek V. The role of lymphocytes in radiotherapy-induced adverse late effects in the lung. Front Immunol 2016;7:591, http://dx.doi.org/10.3389/fimmu.2016.00591.

[34] Midwood KS, Piccinini AM. DAMPening inflammation by modulating TLR signalling. Mediators Inflamm 2010;2010:1–21, http://dx.doi.org/10.1155/2010/672395.

[35] Dulohery MM, Maldonado F, Limper AH, et al. Drug-induced pulmonary disease. In: Mason R, editor. Textbook of respiratory medicine. Saunders; 2016.

[36] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335–7, http://dx.doi.org/10.1016/S1470-2045(20)30096-6.

[37] You B, Ravaud A, Canivet A, Ganem G, Giraud P, Guimbaud R, et al. The official French guidelines to protect patients with cancer against SARS-CoV-2 infection. Lancet Oncol 2020, http://dx.doi.org/10.1016/s1470-2045(20)30204-7.

[38] Zhang H, Huang Y, Xie C. The treatment and outcome of a lung cancer patient infected with SARS-CoV-2. J Thorac Oncol 2020;5(5):e63–79, http://dx.doi.org/10.1016/j.jtho.2020.02.025.

[39] Angelis V, Tippu Z, Joshi K, Reis S, Gronthoud F, Fribbens C, et al. Defining the true impact of coronavirus disease 2019 in the at-risk population of patients with cancer. Eur J Cancer 2020;136:99–106, http://dx.doi.org/10.1016/j.ejca.2020.06.027.

[40] Jin Zhang J, Dong X, Yuan Cao Y, Dong Yuan Y, Bin Yang Y, Qin Yan Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Eur J Allergy Clin Immunol 2020;2020:1–12, http://dx.doi.org/10.1111/all.14238.

[41] Li T, Qiu Z, Zhang L, Han Y, He W, Liu Z, et al. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. J Infect Dis 2004;189:648–51, http://dx.doi.org/10.1086/381535.

[42] He Z, Zhao C, Dong Q, Zhuang H, Song S, Peng G, et al. Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. Int J Infect Dis 2005;9(6):323–30, http://dx.doi.org/10.1016/j.ijid.2004.07.014.

[43] Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 2020;221(11):1762–9, http://dx.doi.org/10.1093/infdis/jiaa150.

[44] He R, Lu Z, Zhang L, Fan T, Xiong R, Shen X, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol 2020;127:104366, http://dx.doi.org/10.1016/j.jcv.2020.104361.

[45] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13, http://dx.doi.org/10.1016/S0140-6736(20)30211-7.

[46] Landman A, Feetham L, Stuckey D. Working together to reduce the burden of pancreatic cancer. Lancet Oncol 2020;21:334–5, http://dx.doi.org/10.1016/S1470-2045(20)30088-7.

[47] Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020;31(7):894–901, http://dx.doi.org/10.1016/j.annonc.2020.03.296.

[48] Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: cancer care in the time of COVID-19. Ann Intern Med 2020;172:756–9, http://dx.doi.org/10.7326/m20-1133.

[49] Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. Nat Rev Clin Oncol 2020;17:268–70, http://dx.doi.org/10.1038/s41571-020-0362-6.

[50] Salako O, Okunade K, Allsop M, Habeebu M, Toye M, Oluyede G, et al. Upheaval in cancer care during the COVID-19 outbreak. Ecancermedicalscience 2020;14:ed97, http://dx.doi.org/10.3332/ecancer.2020.ed97.