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Review Article

Systemic therapy and COVID19: Immunotherapy and chemotherapy

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Abstract

As the novel severe acute respiratory syndrome coronavirus-2 related pandemic - Corona Virus Disease 2019 (COVID-19) has emerged, decision making in the context of cancer treatment has become more complex. The apprehension of using drugs that could adversely affect infected patients, the risk of not using life-saving treatments and the complexities related to the type of cancer itself, all must be taken into consideration before proceeding with treatment. Data from large registries such as COVID-19 and Cancer Consortium, Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) and NCI COVID-19 in Cancer Patients Study will hopefully provide granularity on the outcomes of patients with cancer who are infected with COVID-19. As these efforts are underway, this review aims to shed light on the management of patients with genitourinary malignancies being treated with systemic therapies while infected with COVID-19. © 2020 Published by Elsevier Inc.

Keywords: COVID-19; Genitourinary cancers; Renal cell carcinoma; Prostate cancer; Bladder cancer

1. Introduction

A WHO-designated global pandemic of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged in 2020, infecting more than 20 million people worldwide and leading to more than half a million deaths as of August 14, 2020 [1]. Corona Virus Disease 2019 (COVID-19) can lead to patients presenting with mild disease (respiratory insufficiency) to very severe disease (multiorgan failure). Patients with cancer represent a uniquely vulnerable population in the era of COVID-19 infection. Initial reports from China by Liang et al. reported data on 1,590 patients infected with COVID-19 [2]. They noted higher rates of severe events among cancer patients, with clinically severe numerically higher among patients who underwent chemotherapy or surgery in the previous month [2]. According to the COVID-19 and Cancer Consortium (CCC19), the 30-day all-cause mortality in patients with active or prior cancer and confirmed COVID-19 infection

was 13% [3]. The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry, which includes patients with only thoracic malignancies, reported an even higher mortality rate of 33% [4].

The proposed mechanisms that underlie the increased risk of COVID-19 complications among cancer patients include the immunosuppressive state related to cancer itself, the impact of multiple treatment regimens, as well as coexisting medical disease. Further, patients with genitourinary (GU) cancers are often older, smokers, are treated with drugs that have immunomodulatory effects (programmed cell death 1 [PD-1] or programmed cell death ligand 1 [PD-L1] inhibitors, cytotoxic T-lymphocyte-associated protein 4 inhibitors) and possess unique needs in terms of surgery and perioperative chemotherapy, even in the localized setting. The current review will examine specific considerations to the treatment of GU malignancies in the context of the COVID-19 pandemic.

2. Systemic therapy considerations in the COVID-19 era

The treatment of GU cancers has undergone a paradigm shift over the last few decades. Whereas chemotherapy

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remains important for specific indications, other forms of cancer treatment (e.g., targeted therapies, hormonal therapies, and checkpoint inhibitors) now dominate this space.

2.1. Chemotherapy related challenges in the COVID-19 era

Several unique challenges exist in the treatment of patients with GU cancer suspected of being infected with COVID-19. Whereas a variety of options exist, chemotherapy continues to form the backbone of treatment in certain situations, including docetaxel for advanced prostate cancer or platinum-based chemotherapy for muscle-invasive and advanced bladder cancer [5–8]. For those diagnosed with advanced testicular cancer, chemotherapy remains the only option for patients seeking a potential cure.

The effect of chemotherapy on disease outcomes among patients also infected with COVID-19 remains unclear, with conflicting results emerging from early studies. The aforementioned report from China by Zhang et al. had shown a significantly increased risk of adverse outcomes among those patients who received cancer treatment within the previous 14 days (Table 1) [7]. Notably however, this study reported data on only 28 patients, of which 10% had received chemotherapy. A further larger study from China reported data on 105 patients with cancer who also had a COVID-19 infection. The authors reported a higher rate of death and severe illness among patients who received immunotherapy or had undergone recent oncologic surgery, but not among patients who had received chemotherapy [8]. More recent data from the CCC-19 registry of an initial 928 patients has shown an increased risk of death among cancer patients; however, there was no significant association between systemic therapy in the past 4 weeks and the risk of death or serious complications [3]. Further analyses examining the association between type of systemic therapies and disease outcomes is yet to be published. In data presented from the TERA-VOLT registry, univariate analysis suggested patients receiving treatment with chemotherapy alone were at an increased risk of death; however, this effect was not seen in follow-up multivariate analysis [4]. Whereas this data was limited to patients with thoracic malignancies, the final analysis found no association between type of systemic therapy (targeted agents, chemotherapy and immunotherapy) and survival. Finally, a study conducted by Tang et al., which pooled results from ~400 patients with cancer and COVID-19, demonstrated a significant association between anticancer therapy in the past 4 weeks and death during hospitalization (odds ratio [OR] 3.99; 95%CI 2.08–7.64) [9].

These conflicting results have resulted in a lack of consensus from societies like the American Society of Clinical Oncology and no specific guidelines have been published on the management of patients with cancer and COVID-19. For example, it is unclear how long oncologists should wait before starting chemotherapy once a patient is infected with

COVID-19 because of variable durations of viral shedding among infected individuals [11]. American Society of Clinical Oncology guidelines suggest waiting for infected patients to become asymptomatic and register a negative COVID-19 test before resuming treatment; however this could be challenging in the context of rapidly progressive disease [12]. Whereas withholding chemotherapy is likely required in symptomatic patients with COVID-19 infection, other treatments such as androgen deprivation therapy (ADT) may not need to be delayed among patients with prostate cancer. Ultimately, until there is more definitive data, most of these decisions are left to an individual oncologists' discretion and will thus vary based on patient characteristics, type of cancer being treated, and provider preferences.

Further unique challenges associated with the administration of chemotherapy among patients with cancer in the current COVID-19 era include the risk of exposure to COVID-19 infection during frequent clinic visits for infusion and monitoring, or during hospitalization for serious adverse events. Further, there is a lack of sufficient data at this time to delineate if chemotherapy-related myelosuppression predisposes patients to develop more severe symptoms of COVID-19 infection. Though not supported by clinical trial data, anecdotally, clinicians appear more willing to utilize growth factor support in these scenarios.

2.2. Immunotherapy related challenges in the COVID-19 era

Immune checkpoint inhibitors (ICIs) function by blocking inhibitory receptors on T-cells (cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein-1 [PD-1] inhibitors) or on tumor cells (programmed death–ligand-1 [PD-L1] inhibitors). These drugs form the backbone of treatment regimens for patients with renal cell carcinoma (RCC) and bladder cancer. In metastatic RCC, three randomized clinical trials have established the role of ICIs. These include ipilimumab and nivolumab in CheckMate 214 [13], pembrolizumab and axitinib in KEYNOTE-426 [14] and avelumab and axitinib in JAVELIN Renal 101 [15]. Among bladder cancer patients, atezolizumab and pembrolizumab are approved in the front-line setting for platinum ineligible patients with PD-L1 overexpressing tumors [16,17]. In the postplatinum setting, pembrolizumab remains the preferred agent [18], with other agents (atezolizumab, nivolumab, avelumab, durvalumab) included in treatment guidelines but not supported by randomized, phase III trials [19–23].

The clinical conundrum related to the use of ICIs among patients infected with COVID-19 is more complex and nuanced as compared to the utilization of chemotherapy. This is likely due to the underlying mechanisms of immune modulation, as well as the concern for ICI related adverse events (perhaps most specifically pneumonitis) among those infected with COVID-19. There are varying data to

Table 1
Outcomes in patients with cancer in the context of COVID-19

Author	Study details	Sample size	Key outcomes	Reference
Zhang et al.	<ul style="list-style-type: none"> Retrospective Multiple cancer types 	$n = 28$	<ul style="list-style-type: none"> Mortality rate = 28.6% Receipt of cancer treatment within 14 days led to inferior outcomes No significant difference described between treatment modality (chemotherapy vs. radiation therapy vs. targeted therapy vs. immunotherapy) 	[7]
Kuderer et al.	<ul style="list-style-type: none"> CCC-19 registry Multiple cancer types 	$n = 928$	<ul style="list-style-type: none"> 30-day all-cause mortality was 13% General baseline variables associated with worse outcomes: older age, male sex, 2 or more comorbidities and former smoking status Cancer associated variables associated with worse outcomes: active or measurable cancer, ECOG performance status of 2 or more, progressive cancer 	[3]
Garassino et al.	<ul style="list-style-type: none"> TERAVOLT registry Thoracic malignancies 	$n = 200$	<ul style="list-style-type: none"> Mortality in patients with thoracic cancer is 33% On univariable analyses: age >65 years, being a current or former smoker, receiving treatment with chemotherapy alone, comorbidities were associated with increased risk of death. Upon multivariable analysis, only smoking history was associated with an increased risk of death. Type of systemic therapy (TKIs, chemotherapy, and immunotherapy) did not have an impact on survival 	[4]
Dai et al.	<ul style="list-style-type: none"> Retrospective Multiple cancer types 	$n = 105$	<ul style="list-style-type: none"> Immunotherapy did not worsen outcomes Patients with cancer with worse outcomes Worst outcomes in patients with hematologic malignancies, lung cancer and metastatic disease Immunotherapy and recent surgery led to worse outcomes 	[8]
Lee et al.	<ul style="list-style-type: none"> UK Coronavirus Cancer Monitoring Project (UKCCMP) registry Multiple cancer types 	$n = 800$	<ul style="list-style-type: none"> Mortality rate of 28% Neither chemotherapy nor immunotherapy administered within the past 4 weeks was found to have a significant effect on mortality Worse outcomes are seen with advancing patient age, being male and presence of other comorbidities 	[10]
Liang et al.	<ul style="list-style-type: none"> Retrospective 	$n = 18$	<ul style="list-style-type: none"> Patients with cancer correlated with a higher risk of severe events, including death Numerically higher events in patients who underwent chemotherapy or surgery in the past month 	[2]
Tang et al.	Pooled analysis of study by Yang et al. and Tian et al.	$n = 205$, (Yang et al.) $n = 232$, (Tian et al.)	<ul style="list-style-type: none"> Worse outcomes reported in cancer patients Receipt of chemotherapy, targeted therapy, immunotherapy, or having surgery 2–4 weeks prior to infection reported to be associated with 4x higher risk for inpatient death 	[9]

describe the interaction between treatment with ICIs and viral illness. Pre-clinical data suggest that ICIs can activate cytotoxic T cells and reduce acute viral load in infected patients; however such models also showed the potential for hyperactivation of the immune system and secretion of inflammatory cytokines resulting in immune-mediated

injury [20,21]. At the same time, ICI administration itself has also been reported to cause a state of “immune hyperactivation,” whereby patients present with cytokine release syndrome (CRS) (Fig. 1) [22–28]. This massive release of cytokines can result in symptoms ranging from mild constitutional symptoms (fever, malaise, and myalgias) to severe

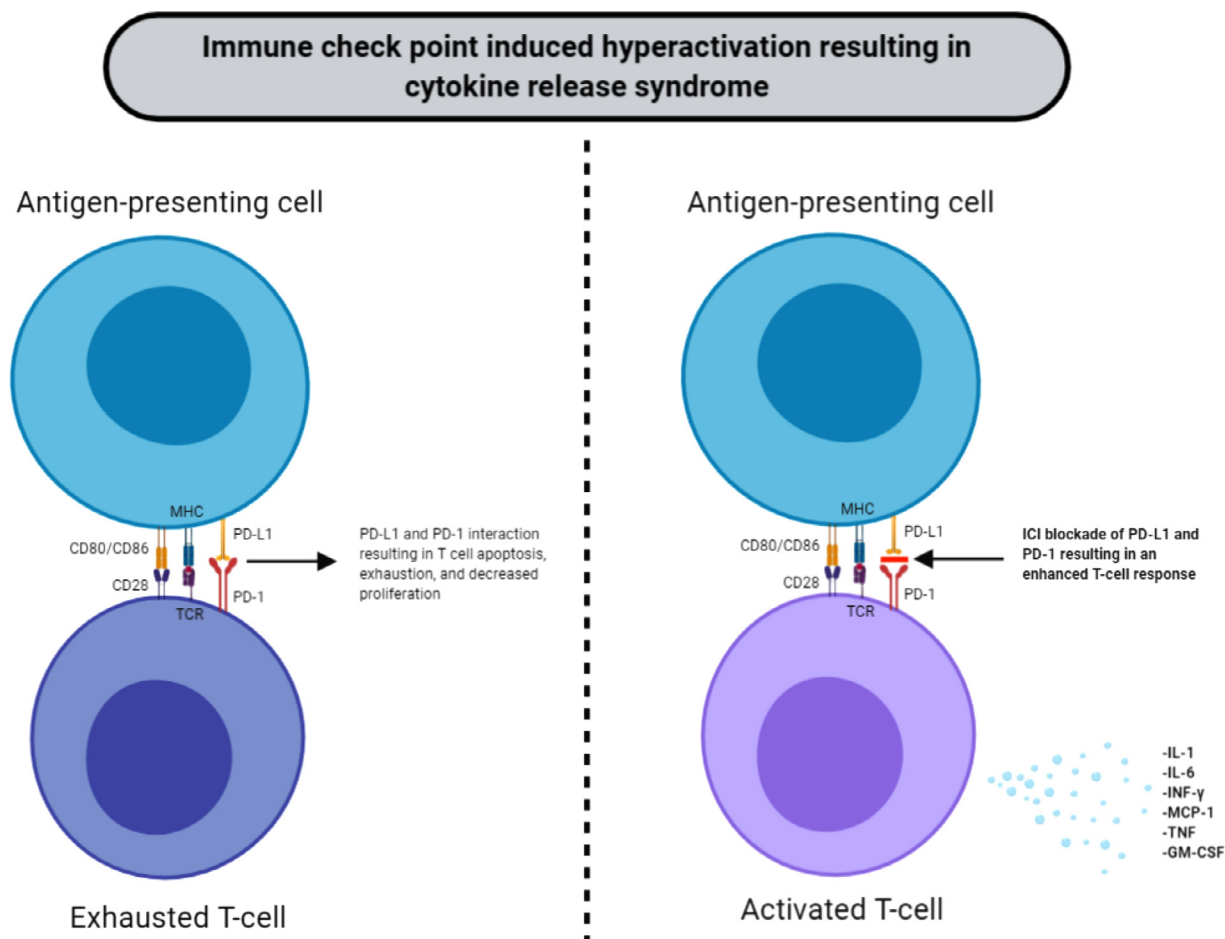


Fig. 1. Potential for cytokine release in the context of immunotherapy. (Figure created with BioRender software, ©biorender.com.)

end-organ damage. A retrospective study from China of 150 patients with confirmed COVID-19 infection showed that elevated ferritin and IL-6 were predictors of death, suggesting that COVID-19 induced immune activation may be a contributing factor in increasing mortality [24]. Theoretically, this could be augmented by ICIs.

A further analysis of 200 patients with thoracic malignancies from the TERAVOLT registry included 23% of patients who were administered ICIs alone and 14% who were on combined chemo-immunotherapy [4]. Treatment with these agents was not associated with an increase in mortality among patients infected with COVID-19. In contrast, a study by Dai et al. noted that 6 of the 105 patients treated with ICIs presented with a more severe clinical course and had an increased risk of mortality [8]. Although this study population consisted of a variety of cancer types, all 6 patients treated with ICIs had thoracic malignancies. Further examination of CCC-19 registry data concerning the impact of ICI based treatment and outcomes has not yet been presented, but will provide important insight and guidance given the large cohort size. The decision to treat patients with one-agent vs. another is not a simple one. In a survey conducted among 41 experts in treating patients

with metastatic RCC, the preferred treatment in patients with favorable risk disease was pembrolizumab/axitinib for 53% independent of the pandemic, while only 35% of the experts chose an ICI based regimen during the COVID-19 pandemic [25].

3. Recommendations for patients with GU malignancies (Fig. 2)

3.1. Bladder cancer

The management of patients with bladder cancer remains complex in the COVID-19 era due to the multiple treatment options, including chemotherapy and ICIs, that are approved by the FDA. There exists no granular data to help guide specific recommendations, however based on current data, it may be prudent to consider the following points. For muscle invasive bladder cancer (MIBC), immediate surgery may not be needed, however there are reports to suggest that a delay of more than 12 weeks in performing a radical cystectomy is associated with poorer outcomes [26]. Similarly, prospective data suggests that administering neoadjuvant chemotherapy prior to surgery is associated

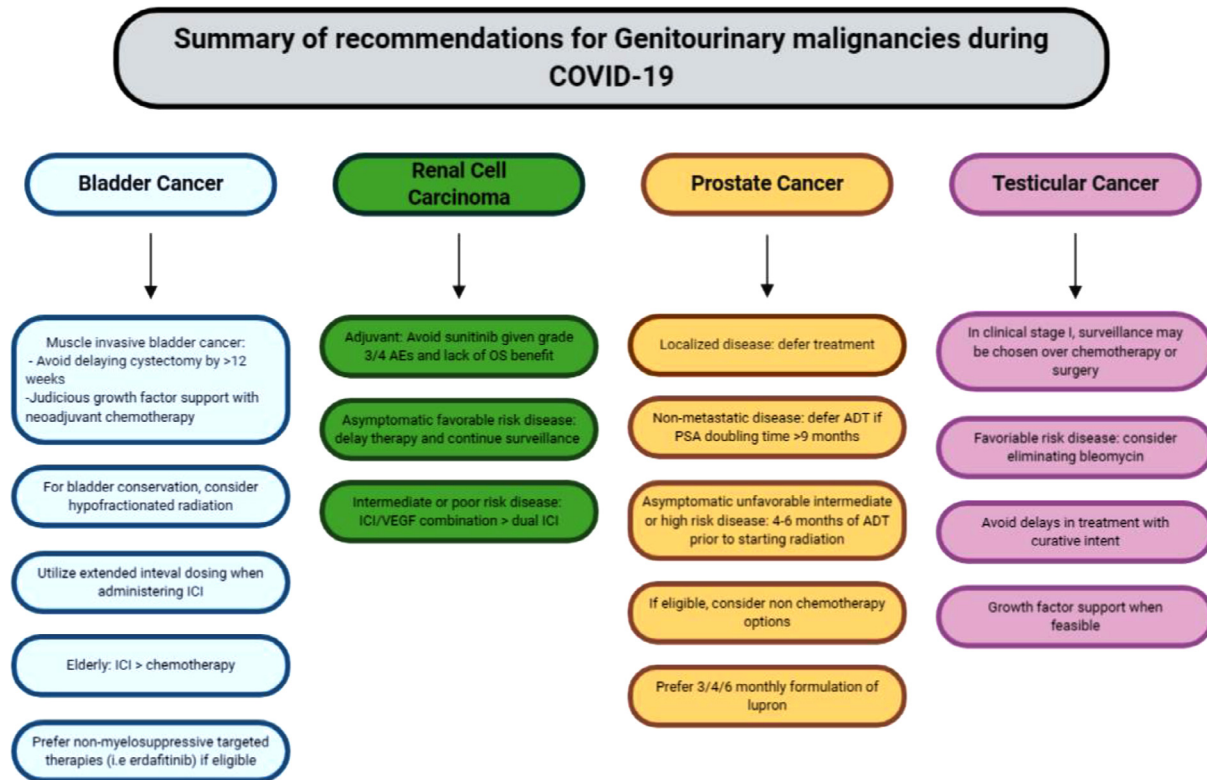


Fig. 2. Systemic therapy recommendations for specific GU cancers in the COVID-19 era.

with improved survival in patients with locally advanced bladder cancer [27]. Therefore, it may be prudent to continue this treatment paradigm and administer neoadjuvant chemotherapy prior to surgery, with aggressive growth factor support to avoid hospitalizations and minimize the risk of exposure to COVID-19. If a bladder preservation technique is being considered for localized, muscle invasive bladder cancer, a hypofractionated radiation schedule may serve to reduce the duration of radiation treatment from ~6.5 weeks to 4 weeks; as these have been shown to be equivalent in a randomized controlled clinical trial [28]. Insufficient data exists regarding whether to utilize chemotherapy or ICI based therapy in the metastatic setting in the context of patients with a coexisting COVID-19 infection; however, the liberal use of growth factor among patients treated with chemotherapy is strongly recommend.

In frail, elderly patients, it might be preferable to use ICI based treatments to avoid myelosuppression and repeat clinic visits or hospitalizations. In order to reduce the burden of repeat visits, one could consider administering pembrolizumab at a 400-mg/6-week dosing schedule, as this regimen is now FDA approved. Targeted agents, such as the FGFR inhibitor erdafitinib, should be the preferred agent among patients with FGFR2/3 alterations, given the low risk of myelosuppression with this agent [29]. In contrast, most myelosuppressive options, such as enfortumab, could be sequenced later.

3.2. Renal cell carcinoma

The management of RCC is similarly not clearly defined among patients also infected with COVID-19. As alluded to previously, according to an international survey of oncologists who manage patients with RCC, utilization of ICI based regimens has become less favored during the pandemic [25]. For localized RCC, it might be pertinent to avoid adjuvant sunitinib, since this drug has not been associated with an increase in overall survival and can result in relatively high rates of grade three-fourth toxicities that would warrant more frequent clinic visits or hospitalization [30]. In patients with favorable risk disease per International Metastatic RCC Database Consortium (IMDC) criteria, delaying therapy with close surveillance may be recommended for patients with minimal disease burden. When such patients are required to start treatment, it may be ideal to start with single agents, such as vascular endothelial growth factor (VEGF) inhibitors. Among patients with IMDC intermediate or poor risk disease, treatment with an ICI/VEGF combination (pembrolizumab/axitinib or avelumab/axitinib) might lower the risk of cytokine release syndrome as compared to dual checkpoint inhibition with nivolumab and ipilimumab. CheckMate-214 trial reported that the nivolumab/ipilimumab combination resulted in high-dose steroid use for roughly 35% of patients. The rate of steroid use in JAVELIN Renal 101 study (avelumab/axitinib) was much lower, approximately 11%, however, the

risk of exposure to COVID-19 must be balanced when making this choice, as avelumab requires administration every 2 weeks. A notable concern with high dose steroid administration for treatment of immune related adverse effects is patients may be at increased risk of contracting viral infections as a result of the immunosuppressive effects [31].

3.3. Prostate cancer

The management of prostate cancer will also vary based on stage and risk categorization. In low-risk localized prostate cancer, it is likely appropriate to defer treatment. As disease staging advances, the use of drugs to inhibit androgen signaling become the backbone of prostate cancer management. There are conflicting reports regarding the benefit or harm of androgen suppression in patients infected with COVID-19. Both transmembrane serine protease 2 (TMPRSS2) and angiotensin converting enzyme 2 (ACE2) are known to be androgen dependent. While TMPRSS2 and ACE2 have been proposed as critical targets that enable the SARS-CoV-2 entry into host cells, further evidence is needed to clarify the role of androgen axis manipulation among patients with prostate cancer [32]. Recommendations from the National Comprehensive Cancer Network (NCCN) note that treatment should be deferred among those with non-metastatic prostate cancer on ADT if the prostate antigen doubling time is >9 months. Providers should consider neoadjuvant ADT for 4 to 6 months in asymptomatic unfavorable intermediate risk and high-risk prostate cancer patients being considered for definitive radiation therapy, as well as using the 3/4/6 month formulations of ADT rather than the monthly injection in order to reduce clinic visits [33]. With regard to chemotherapy, the NCCN guidelines recommend treatment deferment if alternatives, such as hormonal therapies, exist. If however chemotherapy is chosen as a modality, growth factor support should be encouraged.

3.4. Testicular cancer

Among patients with testicular cancer, intuitively, treatment with curative intent should not be delayed. In clinical stage-I patients, active postoperative surveillance should be the preferred strategy over chemotherapy. In more advanced stages, there exists variation among clinicians treating patients with seminomatous and nonseminomatous germ-cell tumors. A recent survey conducted among 53 germ-cell tumor experts from Italy, Europe and Canada showed that approximately 66% of physicians were willing to delay chemotherapy treatment among patients with a COVID-19 infection [34]. When therapy is initiated, bleomycin should be avoided among patients with good risk disease, given the risk of pulmonary toxicity, as there is an even higher risk with the administration of 4 cycles of etoposide-cisplatin (EP) substituted for 3 cycles of bleomycin-etoposide-cisplatin. Notably however, in the survey alluded

to before, 75% and 92% of experts from Italy and Canada still preferred to use 3 bleomycin-etoposide-cisplatin over 4 EP cycles, while 100% of European experts preferred 4 cycles of EP in this context [34]. These results highlight the variability that can exist in the real-world usage of chemotherapy regimens when consensus-driven recommendations are lacking. Finally, the management of intermediate-poor risk disease patients should remain unchanged in the COVID-19 era, with measures (e.g., growth factor) to reduce the risk of complications and hospitalization incorporated as part of treatment.

4. Clinical trials

As per NCCN guidelines, enrollment in clinical trials should be encouraged when feasible. In high-risk tumors types, the opportunity to participate in a clinical trial should not be overlooked. Examples of this include trials of adjuvant targeted therapy in FGFR3-mutated urothelial cancer, with an ongoing study exploring the FGFR3 inhibitor infigratinib in this setting. Given the high risk of recurrence among these patients, participation in trials such as this should still be encouraged.

Type of treatment should also be given consideration in the context of clinical trial enrollment. Trials utilizing regimens that are heavily myelosuppressive might be discouraged, such as the phase III study comparing sacituzumab govitecan with physician's choice of chemotherapy (TROPiCS-04) [35]. In a previous phase II study using sacituzumab govitecan in metastatic urothelial carcinoma that has progressed after platinum and checkpoint inhibitors (TROPHY U-01) the rate of grade 3 and grade 4 neutropenia was 35% [36]. Given the high rates of neutropenia in this study, the experimental arm of TROPiCS-04 could result in substantial myelosuppression, which providers should consider in discussions regarding enrollment.

Cooperative groups such as SWOG have reported suboptimal enrollment in the context of COVID-19 [37]. In response, institutions have incorporated novel approaches, such as telemedicine to continue procedures like obtaining consents and follow-up visits, to promote patient care [38]. Other potential benefits of telemedicine include improving access to healthcare while minimizing the risk of transmission [39]. Further, several investigators have employed remote site initiation visits and interim monitoring visits through online platforms. For example, one study from an academic medical center reported that none of their active study participants were required to stop protocol treatment as a consequence of the pandemic [40].

5. Conclusion

In summary, the uncertainty and lack of clinical evidence regarding the management of patients with cancer and coexisting infection with COVID-19, has raised several important questions. Much of the data presented is based on

the assumption that the virus will peak, however the current trends in both Europe and the US illustrate otherwise. As such, there is an urgent need to report cases to national registries so that information concerning clinical outcomes in the context of each cancer type and treatment can accumulate. Without this data, it will continue to be very difficult for clinicians to assess the safety and efficacy of various treatments in this complex and challenging time. Thus, as evidence builds, we must remain cognizant of how COVID-19 may affect a variety of patient outcomes and continue to refine treatment recommendations as such.

Although COVID-19 vaccine trials have shown promise, their impact on the cancer demographic is yet to be understood. Patients with active cancer or a history of cancer are often excluded from a majority of vaccine studies [41]. Furthermore, there is much uncertainty as to whether treatment, especially immunosuppressive regimens, could affect the ideal time the vaccine should be administered or whether cancer patients will mount an adequate immune response [42]. Further, given this complex clinical picture, providers must engage with patients in a shared decision-making model. It is hoped that as more clinical and pre-clinical data emerges, and findings become more robust, the oncology community will be better prepared to manage the complex clinical scenarios brought forth by the COVID-19 pandemic.

Conflict of Interest

SKP has served as a consultant to Pfizer, Novartis, Aveo, Genentech, Exelixis, Bristol Myers Squibb, Astellas Pharma, GlaxoSmithKline, Eisai, Roche, and Ipsen and received honoraria from Novartis, Medivator, Astellas Pharma. SG, RM, and PB have no conflicts of interest to disclose.

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