Cancer in the context of COVID-19: Summary of emerging evidence (16)

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The CRI presents a selection of emerging research articles and clinical practice guidelines related to cancer and COVID-19, with a summary of their key findings/recommendations (links to the articles are embedded as hyperlinks in the titles). This is the 16th of our weekly compilation, which we plan to update and disseminate as the pandemic evolves globally and nationally.

This week, we highlight the latest research and evidence related to oncology services in COVID-19 outbreak contexts globally, with a focus on African and other low- and middle-income country (LMIC) contexts. We hope that insights from these pieces of evidence will help guide how we rethink cancer prevention, treatment and care in the context of the ongoing pandemic, in view of its unprecedented implications for patients, healthcare providers and the community in general. We are keen to include research and guidelines from African and other low- and middle-income settings and will profile these as they become available. Previous weeks' editions can be found on the **CRI website,** as well as on **our Twitter page (@UctCri)**.

Gougis et al. Anticancer drugs and COVID-19 antiviral treatments in patients with cancer: What can we safely use? Eur J Cancer. DOI: 10.1016/j.ejca.2020.05.027

Country context: Global

This letter to the editor summarises the anticancer drug classes that have been reported to increase either neutropenia or infections, as well as the pharmacokinetic and pharmacodynamic interactions of interest concerning non-immunosuppressive anticancer drugs and potential COVID-19 treatments.

The table below summarizes interactions between antiviral and anticancer drugs.

Part A - Class of anticancer drugs with immunosuppressive properties. Immunosuppressing drugs were defined as drugs associated with significantly more infections or neutropenia compared with the control group or placebo in trials. These drugs were excluded from part B.

Part B - Summary of pharmacokinetic (PK) and pharmacodynamic (PD) interactions of interest concerning non-immunosuppressive anticancer drugs and potential COVID-19 treatments. No interaction driven by other cytochromes was found.

A-

Immunosuppressing classes of drugs					
	Cytotoxic chemotherapy	Proteasome inh.	Histone deacetylase inh.	Anti-CD20	PI3K-AKT-mTOR pathway inh.
	BCR-ABLi	FLT3i	MEKi	JAKi	BTKi
	CDK4-6i	PARPi	Multikinase inh. (sorafenib, sunitinib or others)		

B-

			PK interactions						PD interactions		
			HCQ/CQ	Azithromycin	Lopinavir/r	Toclizumab Interferon-β	Remdesivir	Favipiravir	HCQ/CQ Azithromycin Favipiravir Lopinavir/r	Lopinavir/r	Lopinavir/r Toclizumab Remdesivir
		cytochromes involved in interaction	S3A4	I_h3A4 S3A4	I_h3A4 I_h2D6 S3A4	I_h3A4	I_d1A2 (S3A4)	I_h 2C8	QT	Nephro tox	Liver tox
EGFR	Erlotinib	S3A4 / S1A2		↑	↑	↑	↓				
	Osimertinib	S3A4		↑	↑	↑					
	Cetuximab										
HER2	Trastuzumab										
	Pertuzumab										
	Lapatinib	S3A4 / I_h3A4 / S2C8	↑	↑	↑	↑		↑			
VEGF	Bevacizumab										
	Ramucirumab										
BRAF	Vemurafenib	S3A4 / I_d3A4	↓	↑	↓	↑					
	Dabrafenib	S3A4 / I_d3A4 S2C8	↓	↑	↓	↑	↓	↑			
ALK	Crizotinib	S3A4 / I_h3A4	↑	↑	↑	↑					
	Alectinib										
	Ceritinib	S3A4 / I_h3A4	↑	↑	↑	↑					
FGFR	Erdafitinib	S3A4		↑	↑	↑					
Endocrine therapies	Tamoxifen*	S3A4 / I_d3A4 / S2D6	↓	↓	↓	↓	↓				
	Fulvestrant										
	Anastrozole										
	Letrozole										
	Exemestane										
	Abiraterone	(S3A4) / I_h3A4	↑	↑	↑						
	Enzalutamide	(S3A4) / I_d3A4 S2C8	↓	↓	↓		↓	↑			
	GnRH analogs										
Immuno-therapy	antiPD1/PDL1										

*Tamoxifen is a prodrug and the reported effect is on the active metabolite endoxifen.Red arrows are for interactions relying on clinically significant data. Orange arrows are for interactions relying on in vitro data for pharmacokinetic interactions. Cytochromes involved in the drug interaction were specified. Substrates for which induction but not inhibition could lead to significant interaction are between brackets. When the interaction modifies the pharmacokinetics of the anticancer drug, the arrow was on the bottom-left. Antiviral exposition prediction is on the topright. Red boxes are for anticancer drugs with known torsade de ointes risk and high risk of renal and liver toxicities. Orange boxes are for anticancer drugs prolonging QT without known torsade de pointes risk and moderate risk for renal and liver toxicities. Data from FDA labels [4] were retrieved for drug metabolism, QT prolongation and nephrotoxicity. LiverTox database was used for hepatotoxicity [5].CQ: chloroquine; GnRH: gonadotrophin-releasing hormone; HCQ: hydroxychloroquine; Id : cytochrome inducer; Ih: cytochrome inhibitor; Lopinavir/r: lopinavir/ ritonavir association (KALETRA); S: substrate.

Jafari et al. Considerations for Interactions of Drugs Used for the Treatment of COVID-19 With Anti-Cancer Treatments. Crit Rev Oncol Hematol. DOI: 10.1016/j.critrevonc.2020.102982.

Country Context: Global

This article reviews the available literature on reported drug-drug interactions (DDIs) of some current treatments for COVID-19 and anticancer agents. The key findings are highlighted in the tables below:

Table 1: Chloroquine DDIs

Covid-19 drug	Type of interaction		Result
Chloroquine	Q-T interval prolongation	Apalutamide, Leuprolide, Goserelin, Triptorelin,(Garnick, 2005) Eribulin (Perry, 2011), Ribociclib (Syed, 2017), Inotuzumab (Kebriaei et al., 2018), Gemtuzumab (Selby et al., 2019), Lenvatinib(Frampton, 2016), Dasatinib (Keam, 2008), Nilotinib (Kim et al., 2012), Cabozantinib and Ceritinib (Shah and Morganroth, 2015), Methadone (Barkin et al., 1998) Oxaliplatin(Chang et al., 2013) Ondansetron(Charbit et al., 2005)	Increase Q-T prolongation probability
	CYP3A4 induce	Apalutamide(Pérez-Ruixo et al., 2020), Ivosidenib (Pérez-Ruixo et al., 2020), Fedratinib (Xu) Dabrafenib(Ballantyne and Garnock-Jones, 2013), Encorafenib(Ballantyne and Garnock-Jones, 2013)	Decrease the level of CQ
	CYP3A4 inhibit	Idelalisib(Ballantyne and Garnock-Jones, 2013), Crizotinib(Forde and Rudin, 2012), Fedratinib(Xu et al., 2014), Dasatinib(Haouala et al., 2011), Abiraterone(Benoist et al., 2016), Bicalutamide(Meulenbeld et al., 2013), Aprepitant(Majumdar et al., 2003), Imatinib (Majumdar et al., 2003)	Increase the level of CQ
	CYP2D6 inducers	–	–
	CYP2D6 inhibitors	Dacomitinib(Bello et al., 2012), Abiraterone(Yang, 2011), Ondansetron(Blower et al., 2005), Methadone(Wu et al., 1993)	Increase the level of QC
	Pharmacodynamic synergism	All chemotherapy agents	Myelosuppression
	Pharmacodynamic antagonism	Sipuleucel-T(Cooper and Magwere, 2008; Plosker, 2011)	
	Effect on distribution	MTX(Blower et al., 2005)	

Table 2: Protease inhibitors DDIs

Covid-19 drug	Type of interaction		Result
Protease inhibitors* (Makinson et al., 2010; Pasin, 2015; Rudek et al., 2011)	–	Platinum	No effect
	Inhibition of CYP3A4	Taxans	Increase the level of docetaxel
	Inhibition of CYP3A4	Vincaalkaloids	Increase the level vincaalkaloids
	–	Gemcitabine	No effect
	–	Topotecan	No effect
	Inhibition of CYP3A4	Irinotecan	Increase the level of irinotecan
	–	Pemetrexed	No effect
	–	Bevacizumab	No effect
	–	Cetuximab	No effect
	Inhibition of CYP3A4	Erlotinib	Increase the level of erlotinib
	Inhibition of CYP3A4	Gefitinib	Increase the level of gefitinib
	Inhibition of CYP3A4	Etoposide	Expect to increase the etoposide toxicity
	–	Anthracycline	No effect
	Inhibition of CYP3A4	Everolimus	Increase the level of Everolimus

* It should be mentioned that hyperbilirubinemia can be seen with atazanavir, but is not a guidance for chemotherapy drug adjustment dose (Rudek et al., 2011).

Ivermectin DDIs: There are not enough clinical data about ivermectin drug interactions with non-immunosuppressive anticancer drugs. It is reasonable to cautiously administer ivermectin with drugs that are metabolized by CYP3A4 and induce or inhibit P-glycoproteins.

Remdisivir DDIs: Although there are insufficient data about the drug's pharmacokinetic and drug-drug interactions,. physicians should prescribe this drug with caution when used with multiple medications.

Tocilizumab DDIs: Due to its effect on CYP450 activity, caution must be exercised when co-administering tocilizumab with other agents that are metabolized by CYP450.

Robilotti et al. Determinants of COVID-19 Disease Severity in Patients With Cancer. Nature Medicine. DOI: 10.1038/s41591-020-0979-0

Country Context: USA

This study evaluated the epidemiology of COVID-19 in cancer patients at a tertiary cancer center during the height of the outbreak in New York City. It presents an analysis of risk factors

for severe infection in patients with cancer. From 10 March to 7 April 2020, 423 cases of symptomatic COVID-19 were diagnosed from a total of 2,035 patients with cancer tested. Of these, 40% were hospitalised for COVID-19, 20% developed severe respiratory illness (including 9% who required mechanical ventilation) and 12% died within 30 days. Age older than 65 years and treatment with immune checkpoint inhibitors (ICIs) were predictors for hospitalisation and disease severity, whereas receipt of chemotherapy and major surgery were not.

Table: Predictors of hospitalisation and severe respiratory illness for COVID-19

Variable	**Univariate**		**Multivariate**	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Predictors of hospitalisation, by logistic regression (*n* = 411[a])				
Age (>65 years)	1.81 (1.20–2.72)	0.004	1.53 (0.96–2.43)	0.072
Sex (female)	0.89 (0.60–1.32)	0.575		
Race (non-white)	1.36 (0.91–2.04)	0.135	1.62 (1.05–2.51)	0.029
BMI (≥30 kg/m^2)	0.89 (0.58–1.36)	0.585		
Smoking (current/former)	1.60 (1.07–2.40)	0.022	1.37 (0.88–2.13)	0.169
Asthma/COPD	1.39 (0.81–2.37)	0.226	1.07 (0.59–1.92)	0.828
Cancer (non-metastatic solid)	1.00 (Ref)	-	1.00 (Ref)	
Cancer (metastatic solid)	0.89 (0.53–1.50)	0.647	0.76 (0.43–1.34)	0.338
Cancer (hematologic)	2.24 (1.25–4.06)	0.007	2.49 (1.35–4.67)	0.003
Major surgery (within 30 d)	1.24 (0.53–2.84)	0.612		
Diabetes	1.20 (0.73–1.96)	0.467		
Cardiac disorder	1.86 (1.13–3.07)	0.015	1.35 (0.77–2.36)	0.297
HTN/chronic kidney disease	1.84 (1.24–2.75)	0.003	1.51 (0.96–2.39)	0.077
Systemic chemotherapy (within 30 d)	1.04 (0.70–1.54)	0.845		
Chronic lymphopenia or corticosteroids	1.86 (1.11–3.15)	0.019	1.85 (1.06–3.24)	0.030
ICI	2.53 (1.18–5.67)	0.017	2.84 (1.24–6.72)	0.013
Predictors of severe respiratory illness, by Cox proportional hazard (*n* = 423)				
Variable	**Univariate**		**Multivariate**	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age (>65 years)	2.02 (1.33–3.08)	0.001	1.67 (1.07–2.60)	0.024
Sex (female)	1.04 (0.68–1.58)	0.859		
Race (non-white)	1.20 (0.79–1.84)	0.394		

Variable	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
BMI (≥30 kg/m^2)	1.01 (0.64–1.59)	0.965		
Smoking (current/former)	1.78 (1.17–2.72)	0.007	1.39 (0.89–2.17)	0.148
Asthma/COPD	1.63 (0.98–2.71)	0.059	1.24 (0.72–2.13)	0.436
Cancer (non-metastatic solid)	1.00 (Ref)	-	1.00 (Ref)	-
Cancer (metastatic solid)	0.87 (0.48–1.59)	0.658	0.75 (0.40–1.41)	0.371
Cancer (hematologic)	1.69 (0.92–3.10)	0.092	1.79 (0.97–3.32)	0.063
Major surgery (within 30 d)	1.31 (0.63–2.71)	0.464		
Diabetes	1.09 (0.65–1.83)	0.745		
Cardiac disorder	2.02 (1.28–3.19)	0.002	1.44 (0.88–2.37)	0.147
HTN/chronic kidney disease	1.68 (1.09–2.58)	0.020	1.18 (0.73–1.89)	0.505
Systemic chemotherapy (within 30 d)	1.19 (0.78–1.82)	0.407		
Chronic lymphopenia or corticosteroids	1.59 (0.97–2.59)	0.066	1.42 (0.86–2.34)	0.165
ICI	2.38 (1.29–4.38)	0.005	2.74 (1.37–5.46)	0.004

Mrabti et al. Caring for the Carers: Cancer Management Challenge in a Developing Country in COVID-19 Pandemic: Reflection of a Group of Moroccan Oncologists. Future Oncol. DOI: 10.2217/fon-2020-0450

Country context: Morocco

Following the detection of the first case of COVID-19 in Morocco on 2 March 2020, a panel of oncology experts; consisting of oncologists from universities, regional and private oncology centers in Morocco, was promptly assembled to conduct a group reflection on cancer patients' management. The main objective was to protect the immunocompromised population from the risk of COVID-19, while maintaining an adequate level of the management of cancer. This report shares the reflections and recommendations of the panel of experts. The recommendations are summarised below:

Patients undergoing treatment: the general idea is to focus activity and management on patients under treatment:

- Provide supportive care measures as: G-CSF, erythropoietins for metastatic patients, reduce the use of corticosteroids, switch to zoledronic acid schedule every 12 instead of 4 weeks.
- Protocol adjustments: replace weekly protocols by 3-week regimens, replace cisplatine-based protocols by carboplatin or oxaliplatin (except some curative situations), favor and continue oral regimens: oral chemotherapy, endocrine therapy and oral molecular targeted therapies and space immunotherapy cycles.

- Use telemedicine consultations for patients under oral therapy and plan physical consultation if there is any complication There is the possibility to space Immunotherapy cycles every 4 weeks by keeping the same doses or by increasing the doses: pembrolizumab 400 mg every 6 weeks or atezolizumab 1680 mg every 4 weeks.
- In the curative setting (adjuvant and neoadjuvant): continue chemotherapy, by applying the above adjustments.
- For palliative anticancer treatments: act according to age, the patient's general condition, co-morbidities, type of treatment (chemotherapy, immunotherapy, targeted therapy), line of treatment, stage and prognosis.

New cancer cases:

- New cases should be taken according to the urgency of the situation and the life-threatening prognosis:
    - Screening tests must be stopped during the epidemic.
    - Use the simplest reference check-up as CT scan.
    - Treatment should be initiated according to the urgency of the situation and the risk–benefit balance.
    - In curative situations, opt for therapeutic de-escalation if possible (like endocrine therapy in breast cancer) and indicate high value-added adjuvant chemotherapies.
    - In a metastatic situation, the prognosis is quickly at stake and treatment should be started as soon as possible. Avoid treating elderly patients with co-morbidities and altered general condition, for whom the expected benefit of systemic therapy is low.

Hospitalised patients:

- A readjustment of patients' admission conditions and the adoption of certain precautionary measures after admission are necessary, as follows:
    - Prior to admission, the medical oncologist should be alert for any symptoms that may be related to COVID-19.
    - After admission, certain measures must be put in place to minimise the risk of contamination: reduce the number of doctors visiting patients in bed, comply with the necessary protective measures against coronavirus for the healthcare team and patients, prohibit family visits, provide an isolation room for patients presenting with symptoms of COVID-19 during their stay in the hospitalisation unit.

Palliative care patients:

- Palliative care patients must be kept at home as much as possible, but maintain contact by telemedicine consultation, to adapt treatments or admit them to the hospital if the situation becomes unmanageable at home.

Patients under surveillance:

- Patients should not be brought in for surveillance consultations; unless they present symptoms of recurrence.

Madariaga et al. COVID-19 Testing in Cancer Patients: Does One Size Fit All? Clin Cancer Res. DOI: 10.1158/1078-0432.CCR-20-2224

Country context: Canada

In this perspective article, the authors review the available evidence regarding COVID-19 testing in asymptomatic cancer patients, and describe the approach adopted in a large Cancer Centre in Toronto as a core component of COVID-19 control in their context. They discuss the challenges of detecting asymptomatic carriers, COVID-19 risk assessment strategies for cancer patients and treatment prioritisation strategies based on COVID-19 test outcomes. In addition, they propose a model of care for COVID-19 testing in asymptomatic patients with cancer. The table below summarises the testing priority in asymptomatic cancer patients, in the case of limited testing capacity.

Table: High priority testing characteristics in asymptomatic cancer patients, especially in the event of testing limitations, as per the Ontario Ministry of Health.

High Priority Testing Characteristics
Patients arriving from long-term care facilities, retirement homes, group homes, correction facilities.
Patients with a significant contact with a person with COVID-19, or a household contact with symptoms and not able to defer therapy for 14 days.
Inpatients
Outpatients on radiation/systemic therapy with a risk of immunosuppression from the treatment or underlying disease state and one or more high-risk characteristics: • Age ≥ 60 years • Performance status ≥ 2. • Comorbid conditions (cardiovascular, COPD, diabetes, renal failure) or lymphopenia • Prolonged or severe immunosuppressive regimens • Significant smoking history • Lung tissue in the radiation treatment volume

Shanbhag et al. Managing cancer care during the COVID-19 pandemic - experience at a cancer department in a tertiary hospital in Antigua and Barbuda. Pan African Medical Journal. DOI: 10.11604/pamj.supp.2020.35.2.23092

Country context: Antigua and Barbuda

In this article, the authors illustrate how the COVID-19 pandemic has affected their oncology department in a tertiary cancer treatment centre. They describe the changes in treatment decisions for outpatient and inpatient services, while discussing the ethical considerations, the well-being of the oncology team and the way forward.

News

Amber Court. Fear of contracting Covid-19 delaying cancer patients' treatment at Groote Schuur. IOL News. 4 July 2020

Country context: South Africa

This news article reports on how the fear of contracting COVID-19 may be leading to delays in the number of new cancer patients referred to Groote Schuur Hospital in the last two

months. It shares some views on this observed trend, from both patient and healthcare provider perspectives.

Kevin Brandt. COVID-19 research helps clear young patient ahead of cancer treatment. Eye Witness News. 25 June 2020

Country context: South Africa

This news report narrates how virologists from the University of the Western Cape and Stellenbosch University have recently cultured live samples of the novel coronavirus in a highly controlled laboratory at Tygerberg Hospital. This was done to ascertain if there was still significant viraemia after the child had tested positive for SARS-CoV-2 by RT-PCR 2-3 weeks after symptomatic recovery – a situation that complicated decisions on whether or not treatment should be started. Treatment was eventually started when culture yielded no viral growth.