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Association of Antineoplastic Therapy With Decreased SARS-CoV-2 Infection Rates in Patients With Cancer

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IMPORTANCE Novel therapies for SARS-CoV-2 infection are urgently needed. Antineoplastic compounds that target cellular machinery used by SARS-CoV-2 for entry and replication, including angiotensin-converting enzyme 2 (ACE2), may disrupt SARS-CoV-2 activity.

OBJECTIVES To determine whether patients with cancer treated with potential ACE2-lowering antineoplastic compounds exhibit lower SARS-CoV-2 infection rates.

DESIGN, SETTING, AND PARTICIPANTS We used the Library of Integrated Network-Based Cellular Signatures database to identify antineoplastic compounds associated with decreased *ACE2* gene expression across cell lines. We then evaluated a retrospective cohort of 1701 patients who were undergoing antineoplastic therapy at Memorial Sloan Kettering Cancer Center in New York, New York, during the COVID-19 pandemic to determine if treatment with an ACE2-lowering antineoplastic was associated with a decreased odds ratio (OR) of SARS-CoV-2 infection. Patients included in the analysis underwent active treatment for cancer and received a SARS-CoV-2 test between March 10 and May 28, 2020.

MAIN OUTCOME AND MEASURE The association between potential ACE2-lowering antineoplastic treatment and a positive SARS-CoV-2 test.

RESULTS In the cohort of 1701 patients, SARS-CoV-2 infection rates were determined for 949 (55.8%) female and 752 (44.2%) male patients (mean [SD] age, 63.1 [13.1] years) with diverse cancers receiving antineoplastic therapy. In silico analysis of gene expression signatures after drug treatment identified 91 compounds associated with downregulation of ACE2 across cell lines. Of the total cohort, 215 (12.6%) patients were treated with 8 of these compounds, including 3 mTOR/PI3K inhibitors and 2 antimetabolites. In a multivariable analysis of patients who received an ACE2-lowering antineoplastic adjusting for confounders, 15 of 215 (7.0%) patients had a positive SARS-CoV-2 test compared with 191 of 1486 (12.9%) patients who received other antineoplastic therapies (OR, 0.53; 95% CI, 0.29-0.88). Findings were confirmed in additional sensitivity analyses including cancer type, steroid use, and a propensity-matched subcohort. Gemcitabine treatment was associated with reduced SARS-CoV-2 infection (OR, 0.42; 95% CI, 0.17-0.87).

CONCLUSIONS AND RELEVANCE In this cohort study, in silico analysis of drug-associated gene expression signatures identified potential ACE2-lowering antineoplastic compounds, including mTOR/PI3K inhibitors and antimetabolites. Patients who received these compounds exhibited statistically significantly lower rates of SARS-CoV-2 infection compared with patients given other antineoplastics. Further evaluation of the biological and clinical anti–SARS-CoV-2 properties of identified antineoplastic compounds is warranted.

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Supplemental content

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SARS-CoV-2 is a single-stranded RNA virus that causes COVID-19.[1] SARS-CoV-2 infects host cells by attaching spike glycoproteins to angiotensin-converting enzyme 2 (ACE2), encoded by the *ACE2* gene, expressed on airway epithelia.[1-3] Hemagglutinin cleavage of ACE2 initiates viral internalization and subsequent viral S protein cleavage through hijacking of cellular machinery.[1] Patients with cancer are especially vulnerable to adverse COVID-19 outcomes after SARS-CoV-2 infection.[4]

Engineered anti-ACE2 therapies have demonstrated preliminary success as COVID-19 treatments.[5,6] Repurposed antineoplastic agents that inhibit proliferative signaling pathways hijacked by SARS-CoV-2 are predicted with in silico and in vitro analyses to inhibit SARS-CoV-2 activity, yet clinical activity is rarely evaluated.[7-13]

In this cohort study, we used the Library of Integrated Network-Based Cellular Signatures (LINCS) program to identify antineoplastic compounds associated with decreased *ACE2* gene expression in silico.[14] We then evaluated if patients with cancer treated with potential ACE2-lowering antineoplastics during the COVID-19 pandemic exhibited decreased incidence of SARS-CoV-2 infection.

Key Points

Question Will patients with cancer treated with antineoplastic compounds associated with lower angiotensin-converting enzyme 2 (ACE2) expression exhibit lower SARS-CoV-2 infection rates?

Findings In an in silico analysis of the Library of Integrated Network-Based Cellular Signatures database, 91 compounds were associated with gene downregulation of the ACE2 entry receptor for SARS-CoV-2, including mTOR/PI3K inhibitors and antimetabolites. Patients who received a potential ACE2-lowering antineoplastic exhibited a statistically significantly reduced SARS-CoV-2 positivity rate of 7.0% compared with 12.9% in patients who received other antineoplastic therapies.

Meaning Potential ACE2-lowering antineoplastics, including mTOR/PI3K inhibitors and antimetabolites, may exhibit clinical anti–SARS-CoV-2 activity.

Methods

In Vitro Modeling and Analysis

The LINCS program aggregates quality-controlled in vitro compound screens to identify the gene expression profile of a drug across multiple cell lines (eMethods in the Supplement). Using LINCS, we analyzed *ACE2* gene expression signatures of 1835 compounds across 7 cell lines with the highest gene expression profiles (MCF7, PC-3, HeLa, HT-29, A-375, HA1E, and YAPC). For each compound, a generalized linear model of *ACE2*-moderated *z* scores (weighted average of experimental sample replicates) vs log10(drug concentration) produced model coefficients representing the association between drug treatment and consensus net *ACE2* expression change across all cell lines. The Benjamini-Hochberg (BH) method was used to adjust for multiplicity. Antineoplastic compounds associated with both a negative model coefficient (downregulated *ACE2* expression) and a BH-adjusted $P \leq .10$ were selected for clinical validation.

Patient Cohort and Analysis

Electronic medical record data was obtained from a standardized-input database for adult patients at Memorial Sloan Kettering Cancer Center in New York, New York, who were undergoing antineoplastic treatment for active cancer during the COVID-19 pandemic from March 10 through May 28, 2020. All patients included in the study underwent SARS-CoV-2 real-time polymerase chain reaction testing during this period. Antineoplastics given to patients were categorized per standard definitions (eTable 1 in the Supplement). Patients were stratified based on whether they received a compound associated with a reduced *ACE2* gene expression signature between March 10 and May 28, 2020. Exploratory clinical outcomes, including hospital admission, hypoxic event (≥3 L of supplemental oxygen required), and death, were compiled. Race and ethnicity were derived from patient selections on standardized forms that were uploaded into the electronic medical records. Groups in the Non-White or Hispanic category included patients who selected East Asian or the Indian subcontinent, Black or African American, American Indian or Alaska Native, and other race. Patients who selected both White and Hispanic in the ethnicity section were included in the Non-White or Hispanic category. Patients who selected White and either non-Hispanic or did not enter a value in ethnicity were categorized as White. This study was approved by the Memorial Sloan Kettering Cancer Center institutional review board with exemption of patient consent secondary to use of deidentified data.

Statistical Analysis

The associations between SARS-CoV-2 positivity and study covariates, including ACE2-lowering antineoplastic therapy, were separately evaluated using Fisher exact testing. For univariable analyses, false discovery rate–adjusted *P* values were obtained using the BH method for multiplicity correction. A multivariable logistic regression model evaluated the association between covariates and SARS-CoV-2 positivity (smoking status was excluded owing to excessive missing data). This process was replicated in additional sensitivity analyses to evaluate alternative LINCS thresholds for ACE2-lowering antineoplastic selection, associations between cancer types among patients, steroid use, or ACE2-inducing antineoplastic use and SARS-CoV-2 infection, and a propensity score–matched subcohort analysis (eMethods in the Supplement). Associations between ACE2-lowering antineoplastic status and clinical outcomes were assessed using Fisher exact testing in the overall study cohort and in patients who tested positive for SARS-CoV-2. Analyses were performed using R, version 4.0.0 (R Foundation for Statistical Computing) (eAppendix in the Supplement).

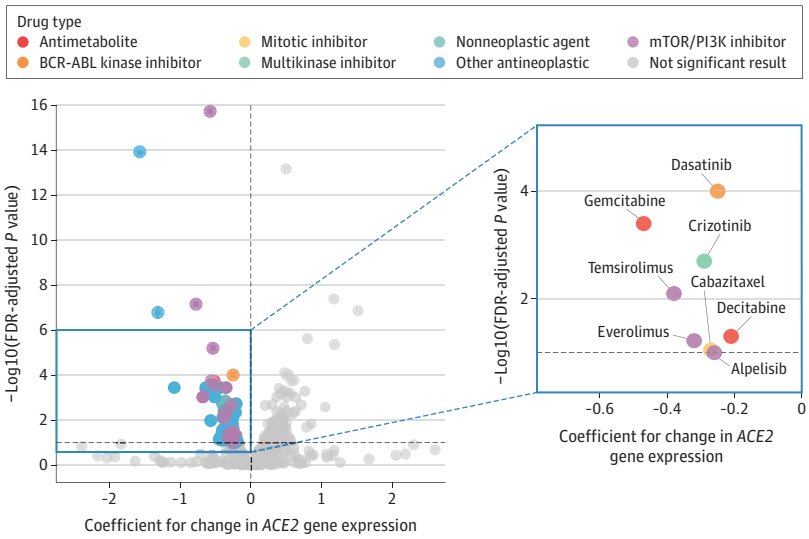
Results

A total of 91 compounds were identified from the LINCS data set (**Figure 1** and eTables 2 and 3 in the Supplement) and associated with considerably reduced *ACE2* gene expression

across cell lines. Of these 91 compounds, 8 were administered in the clinical cohort (Figure 1 and eTables 3 and 4 in the Supplement). Compounds included mTOR/PI3K inhibitors (everolimus, temsirolimus, and alpelisib), antimetabolites (decitabine and gemcitabine), mitotic inhibitors (cabazitaxel), and other kinase inhibitors (dasatinib and crizotinib).

Of the 1701 patients in the study cohort, 1553 (91.3%) possessed solid tumors, although 394 (23.2%) patients had a he-

Figure 1. Identification of Compounds Associated With a Reduced *ACE2* Gene Expression Signature in the LINCS Data Set



A total of 1835 compounds and their respective *ACE2* gene expression signature coefficients (negative value indicates reduced expression; positive value, increased expression) obtained from the Library of Integrated Network-Based Cellular Signatures (LINCS) data set are each represented by circles. Circles are colored according to drug mechanism of action. The y-axis indicates the negative log of the false discovery rate (FDR)-adjusted *P* value associated with each compound's *ACE2* gene signature. Antineoplastics associated with an FDR-adjusted $P \leq .10$ in the LINCS analysis (dotted horizontal line cutoff) also given to patients in the clinical cohort are represented in the zoomed-in partition.

Table. Characteristics of the Clinical Cohort

Covariate	No. (%)[a]		
	All patients (N = 1701)	No ACE2-lowering antineoplastic use (n = 1486)	ACE2-lowering antineoplastic use (n = 215)
Demographics			
Sex			
Female	949 (55.8)	811 (54.6)	138 (64.2)
Male	752 (44.2)	675 (45.4)	77 (35.8)
Race and ethnicity			
White non-Hispanic	1222 (71.8)	1062 (71.5)	160 (74.4)
Non-White or Hispanic[b]	423 (24.9)	372 (25.0)	51 (23.7)
Unknown[c]	56 (3.3)	52 (3.5)	4 (1.9)
Age, y			
≥65	835 (49.1)	724 (48.7)	111 (51.6)
<65	866 (50.9)	762 (51.3)	104 (48.4)
Smoking status			
Current or prior	670 (39.4)	584 (39.3)	86 (40.0)
Never	798 (46.9)	698 (47.0)	100 (46.5)
Unknown[c]	233 (13.7)	204 (13.7)	29 (13.5)
Disease characteristics			
Solid tumor[d]	1553 (91.3)	1355 (91.2)	198 (92.1)
Hematologic cancer[d]	394 (23.2)	356 (24.0)	38 (17.7)
Metastatic disease	654 (38.4)	572 (38.5)	82 (38.1)
Nonmetastatic disease	1047 (61.6)	914 (61.5)	133 (61.9)
Clinical outcomes			
SARS-CoV-2 positive	206 (12.1)	191 (12.9)	15 (7.0)
Not SARS-CoV-2 positive	1495 (87.9)	1295 (87.1)	200 (93.0)
Hospital admission	558 (32.8)	485 (32.6)	73 (34.0)
Hypoxic event	65 (3.8)	56 (3.8)	9 (4.2)
Death	132 (7.8)	109 (7.3)	23 (10.7)

Abbreviation: ACE2, angiotensin-converting enzyme 2.

[a] Patients are stratified based on exposure to potential ACE2-lowering antineoplastic therapy during the study period.

[b] The Non-White or Hispanic category includes patients who self-selected East Asian or the Indian subcontinent, Black or African American, American Indian or Alaska Native, other race, or White and Hispanic.

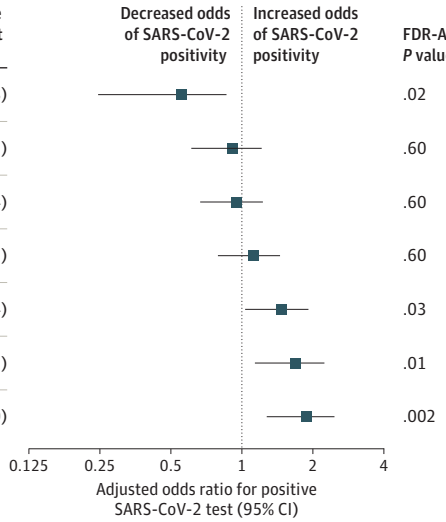
[c] Data were not recorded in electronic medical records.

[d] Indicates categories of patients that are not mutually exclusive.

Figure 2. Association Between Patient Characteristics and SARS-CoV-2 Positivity in Univariable and Multivariable Analyses

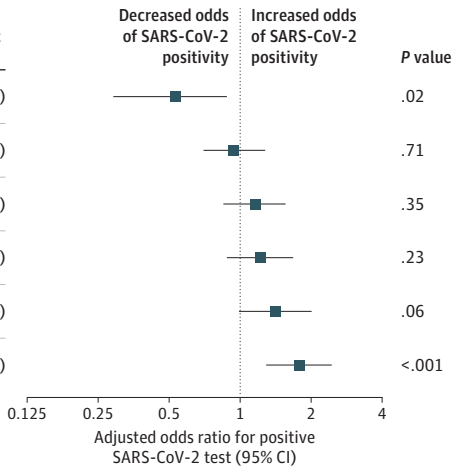
A Univariable analyses

Covariate category	Covariate	No. patients with SARS-CoV-2 positivity/total No. patients (%)	Adjusted odds ratio for positive SARS-CoV-2 test (95% CI)	FDR-Adjusted *P* value
ACE2-lowering antineoplastic use	No ACE2-lowering antineoplastic	191/1486 (12.9)	0.51 (0.27-0.88)	.02
	ACE2-lowering antineoplastic	15/215 (7.0)		
Smoking status	No smoking	101/798 (12.7)	0.88 (0.63-1.23)	.60
	Current or prior smoker	76/670 (11.3)		
Sex	Male	95/752 (12.6)	0.92 (0.68-1.24)	.60
	Female	111/949 (11.7)		
Age	<65 y	101/866 (11.7)	1.09 (0.81-1.47)	.60
	≥65 y	105/835 (12.6)		
Metastatic disease	No metastatic disease	111/1047 (10.6)	1.43 (1.06-1.94)	.03
	Metastatic disease	95/654 (14.5)		
Hematologic cancer	No hematologic cancer	141/1307 (10.8)	1.63 (1.17-2.27)	.01
	Hematologic cancer	65/394 (16.5)		
Race and ethnicity	White non-Hispanic	128/1222 (10.5)	1.81 (1.31-2.50)	.002
	Non-White or Hispanic	74/423 (17.5)		



B Multivariable analysis

Covariate category	Covariate	Adjusted odds ratio for positive SARS-CoV-2 test (95% CI)	*P* value
ACE2-lowering antineoplastic use	No ACE2-lowering antineoplastic	0.53 (0.29-0.88)	.02
	ACE2-lowering antineoplastic		
Sex	Male	0.94 (0.70-1.28)	.71
	Female		
Age	<65 y	1.16 (0.85-1.56)	.35
	≥65 y		
Metastatic disease	No metastatic disease	1.22 (0.88-1.68)	.23
	Metastatic disease		
Hematologic cancer	No hematologic cancer	1.41 (0.99-2.01)	.06
	Hematologic cancer		
Race and ethnicity	White non-Hispanic	1.78 (1.28-1.45)	<.001
	Non-White or Hispanic		



Odds ratios for a positive SARS-CoV-2 test are represented for the second covariate subgroup in comparison with the first covariate subgroup. False discovery rate (FDR)-adjusted *P* values are represented after Benjamini-Hochberg correction for multiplicity (A), and all covariates were placed into a multivariable logistic regression model (B), except smoking status owing to excessive missing data (233 of 1701 patients). Patients with unspecified race and ethnicity were not included in the multivariable analysis (56 of 1701 patients).

matologic cancer, and 312 (18.3%) patients had more than 1 cancer type (**Table** and eTable 4 in the Supplement). A total of 215 (12.6%) patients were treated with a potential ACE2-lowering antineoplastic (Table). Patients in the ACE2 treatment subgroups exhibited similar characteristics, although the ACE2-lowering antineoplastic subgroup was composed of both fewer male patients and patients with hematologic cancers (Table and eTable 4 in the Supplement).

Patients who received an associated ACE2-lowering antineoplastic drug exhibited a statistically significant decreased SARS-CoV-2 positivity rate of 7.0% (15 of 215 patients) compared with a 12.9% rate (191 of 1486 patients) in those not treated with an ACE2-lowering antineoplastic in a multivariable analysis (odds ratio [OR], 0.53; 95% CI, 0.29-0.88; **Figure 2**). This association was consistent in sensitivity analyses that used different LINCS data set significance thresholds to select ACE2-lowering antineoplastics (eTable 5 in the Supplement), as well as separate multivariable analyses that included specific patient cancer types (eTable 6 in the Supplement) or steroid use (eTable 7 in the Supplement), and a propensity score–matched multivariable regression sensitivity analysis that analyzed paired patients based on multiple characteristics (eTable 8 in the Supplement). Non-White or Hispanic patients with cancer exhibited increased SARS-CoV-2 infections compared with White non-Hispanic patients (OR, 1.78; 95% CI, 1.28-2.45).

In the primary analysis, use of gemcitabine was associated with decreased SARS-CoV-2 positivity (OR, 0.42; 95% CI, 0.17-0.87; eTable 9 in the Supplement). Use of ACE2-lowering antineoplastics was not statistically significantly associated with hospital admission, hypoxic event, or death in the overall cohort (eTable 10A in the Supplement) or SARS-CoV-2 positive–only subcohort (eTable 10B in the Supplement).

Discussion

This study used a genomic data set to identify antineoplastic compounds associated with modulation of infectious disease–related gene expression. In a large cohort with diverse cancer and treatment histories, patients who received potential ACE2-lowering antineoplastics were nearly half as likely to have positive results for SARS-CoV-2 compared with patients treated with other active antineoplastic therapies (Figure 2). This finding remained consistent after accounting for confounders in multivariable and propensity score–matched analyses (Figure 2B and eTables 5-8 in the Supplement). Examination of each study drug shows that the majority of associated ACE2-lowering antineoplastics (6 of 8) were associated with at least an absolute 3% reduction in SARS-CoV-2 positivity (eTable 9 in the Supplement). Although individual drug analyses were likely underpowered, patients given gemcitabine demonstrated statistically significant lower SARS-CoV-2 positivity rates compared with patients given other antineoplastics (eTable 9 in the Supplement).

The ACE2-lowering compounds may alter SARS-CoV-2 activity through ACE2-downregulation and/or other plausible antiviral mechanisms. Most associated ACE2-lowering compounds target internal cellular machinery responsible for proliferation and metabolism, similar to kinase inhibitors targeting BCR-ABL, Janus kinase 1 and 2, and Bruton tyrosine kinase currently under clinical validation.[8,9] Everolimus, temsirolimus, and alpelisib inhibit the viral mTOR/PI3K signaling pathway that modulates immune signaling and coronavirus-family viral protein activity in vitro.[10-12] In addition, use of gemcitabine and dasatinib has been shown in vitro to considerably inhibit coronavirus-family viral activity.[7] Gemcitabine and decitabine exhibit similar antimetabolic activity to that of 6-mercaptopurine, which is identified as a SARS-CoV-2 protein inhibitor.[13] Antimetabolite use has been associated with lower COVID-19–related mortality in patients with cancer.[15]

Limitations

This study identifies novel antineoplastic compounds that may impede SARS-CoV-2 activity and subsequently demonstrates a clinical association between compound administration and reduced SARS-CoV-2 infection in a large cohort of at-risk patients with cancer. However, the study has several limitations. Although patients who tested positive for SARS-CoV-2 infection who were given ACE2-lowering antineoplastics exhibited decreased hospital admissions and hypoxic events, these associations were not statistically significant, potentially because of low numbers of observed events (eTable 10 in the Supplement). Mortality from active cancer vs SARS-CoV-2 infection was also difficult to assess. The ACE2-lowering antineoplastics were discovered by computer modeling of in vitro data. Compound mechanism of activity against SARS-CoV-2 is not fully characterized and requires experimental validation, particularly with testing in respiratory epithelial cell lines, which are not well represented in LINCS. Potential protective effects from ACE2-lowering antineoplastics must also be taken in the context of additional immune protection advances that occurred poststudy, including vaccination. The study is hypothesis generating and serves to direct further experimental exploration of the molecular mechanisms underlying anti–SARS-CoV-2 activity for potential ACE2-lowering antineoplastic agents.

Conclusions

In this cohort study, mTOR/PI3K inhibitors and antimetabolites were among several antineoplastic compounds associated with decreased *ACE2* gene expression in silico. Patients with cancer treated with predicted ACE2-lowering antineoplastics exhibited statistically significant lower incidence of SARS-CoV-2 infection compared with patients who received other therapies.

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Concept and design: Foote, White, Diaz Jr.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Foote, White, Wan, Diaz Jr.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Foote, White, Wan, Rousseau.
Administrative, technical, or material support: Foote, White, Jee, Pessin.
Supervision: Foote, Diaz Jr.

Conflict of Interest Disclosures: Dr White reported personal fees from Memorial Sloan Kettering Cancer Center during the conduct of the study and is the founder and owner of Resphera Biosciences LLC. Dr Jee holds a patent licensed by MDSeq Inc. Dr Argilés has received honoraria for advisory roles from Hoffmann-La Roche, Bayer, Amgen, Merck, Sanofi, and Servier; honoraria for speaking engagements from Hoffmann-La Roche, Bristol Myers Squibb, Bayer, and Servier; travel grants from Hoffmann-La Roche, Bayer, Servier, Amgen, and Merck; and research funds from Bayer. Dr Argilés also serves as an uncompensated advisor for Menarini and Treos Bio Inc. Dr Wan is an inventor of patents for methods for circulating tumor DNA detection. Dr Rousseau reported personal fees from Bayer and Roche, as well as nonfinancial support from Servier outside the submitted work. Dr Diaz Jr is a member of the board of directors of Personal Genome Diagnostics (PGDx) and Jounce Therapeutics; a paid consultant to PGDx, 4Paws Dx, Innovatus Capital Partners, Se'er, Kinnate Biopharma, and NeoPhore; an uncompensated consultant for Merck but has received research support for clinical trials from Merck; an inventor of multiple licensed patents related to technology for circulating tumor DNA analyses and mismatch repair deficiency for diagnosis and therapy from Johns Hopkins University, therefore some of these licenses and relationships are associated with equity or royalty payments directly to Johns Hopkins University and Dr Diaz Jr; and an equity holder in PGDx, Delfi Diagnostics, Jounce Therapeutics, Thrive Earlier Detection, and Neophore. No other disclosures were reported.

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