Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Exman P, Bonadio R C., et al., 2024. USE OF REPOURPOSED DRUGS LOSARTAN AND IVERMECTIN IN PATIENTS WITH CANCER FOR PREVENTION OF COVID-19 SERIOUS EVENTS DURING PANDEMIC. A randomized, double-blind, placebo-controlled phase II study. Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5281

DOI:
https://doi.org/10.18103/mra.v12i4.5281

ISSN: 2375-1924

RESEARCH REPORT

USE OF REPOURPOSED DRUGS LOSARTAN AND IVERMECTIN IN PATIENTS WITH CANCER FOR PREVENTION OF COVID-19 SERIOUS EVENTS DURING PANDEMIC. A randomized, double-blind, placebo-controlled phase II study.

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ABSTRACT

Introduction: Cancer patients are at higher risk of COVID-19 severe complications and also demonstrated a lower antibodies conversion after vaccination. Therefore, therapeutic approaches after COVID-19 infection are needed in this population. Repurposing drugs has emerged as an appealing strategy during pandemic, and drugs such as angiotensin 2 antagonists and ivermectin may have a role against COVID-19.

Objective: This trial evaluated losartan plus ivermectin aimed at decreasing the incidence of severe outcomes due to coronavirus infection among cancer patients.

Methods: This was a randomized, double-blind, and placebo-controlled phase II study. Cancer patients with recent diagnosis of mild to moderate COVID-19 were randomized to receive 50 mg of losartan for 15 days plus a single dose of 12 mg of ivermectin or placebo. The primary endpoint was the incidence of severe complications, defined as a need for admission to the intensive care unit (ICU), need for mechanical ventilation (MV), or death. Secondary endpoints were safety and adherence.

Results: Thirty-five patients were randomized to intervention arm and 34 to placebo arm. Seven (20%) patients in the losartan + ivermectin arm experienced severe outcomes versus 8 (23.5%) patients in the placebo arm (p = 1.00). No difference was observed in the need for intensive care unit (17.1% versus 17.6%; p = 1.00) or in the need for mechanical ventilation (17.1% versus 11.8%; p = 0.73). Four patients died in the losartan + ivermectin arm, while 3 in the placebo arm (11.4% versus 8.8%; p = 1.00). Severe adverse events and adherence were similar between groups.

Conclusions and Relevance: The combination of losartan and ivermectin did not improve severe COVID-19 outcomes among cancer patients. This is the first study registered on ClinicalTrials.gov that evaluates active treatment for COVID-19 exclusively for cancer patients. and more studies should be performed for a more aggressive approach in this high-risk population.

Keywords: COVID-19, cancer, losartan, ivermectin, repurposing drugs

Introduction

The World Health Organization (WHO) recognized COVID-19, an infectious respiratory disease caused by the novel coronavirus (SARS-CoV-2), as a pandemic in March 2020 [1]. To date, SARS-CoV-2 is responsible for more than 637,874,040 cases and 6,606,212 deaths worldwide (November 7, 2022, 10:00 GMT; https://www.worldometers.info/coronavirus/).

Complete genomic sequencing and phylogenetic analysis indicated that SARS-CoV-2 is an RNA betacoronavirus of the same subgenre as the severe acute respiratory syndrome (SARS) virus. The structure of the receptor-binding region is very similar to that of the SARS coronavirus, and SARS-CoV-2 has been shown to bind to the receptor of angiotensin-converting enzyme 2 (ACE-2) to enter cells[2].

Clinical manifestations of SARS-CoV-2 infections vary from mild to critical, and most cases are not serious[3-5]. Chinese data on 44,500 confirmed infections showed mild to moderate cases in 81% of patients, severe illness (with dyspnoea, hypoxia or involvement of more than 50% of the lungs) in 14%, and critical illness with respiratory failure in 5% of patients[6]. The overall lethality rate varies between 2.3 and 7.9%, and most deaths occur among patients with advanced age or underlying medical comorbidities[6-10].

Data for the management of cancer patients diagnosed with COVID-19 are still scarce. Liang et al. (2020) demonstrated that cancer patients have a higher risk of serious events than cancer-free patients: 39% versus 8%, respectively ($p = 0.0003$). In addition, patients undergoing chemotherapy or oncological surgery within one month of admission for COVID-19 had a higher probability of developing severe complications or death than patients without cancer[11-13].

Unprecedentedly rapid vaccine development has changed the paradigm of the COVID-19 pandemic, and the number of cases and deaths has been systematically dropping. Unfortunately, such achievements in vaccination did not prove to be proportionally as effective for immunocompromised patients, and cancer patients have demonstrated lower conversion of neutralizing antibodies when compared to the general population, thus showing a higher susceptibility to death due to SARS-CoV-2 in this subpopulation, even when fully vaccinated[14].

Consequently, an aggressive therapeutic approach against COVID-19 is needed for these more vulnerable patients, and drug reallocations–the use of drugs for diseases for which they were not primarily developed–seem to be necessary, especially in the context of a pandemic.

Angiotensin II receptor antagonists (ARA2s), such as telmisartan or losartan, present interesting adjuvant activity for SARS-CoV-2 experimental treatment as reallocated drugs. These drugs mitigate the effects of the imbalance between angiotensin 1 and angiotensin 2 caused by viral infection, which is one of the main mechanisms of lung and myocardial injury by COVID-19[15,16]. Clinical trials of these drugs have demonstrated mixed results in both mild and severe patients. However, high-risk cancer patients were not included in these studies[17-19].

Ivermectin has also been studied as a reallocated drug for COVID-19 infection due

to its integrase protein and importin inhibition activity [20-24], but most of the data originate from poor-quality retrospective studies or highly heterogeneous meta-analyses, and high-quality data for its use in clinical practice are still lacking. To date, two randomized trials have shown no benefit of the use of ivermectin for COVID-19 patients, but oncological patients were also not fully represented[25].

In this double-blind, randomized and placebo-controlled phase II trial, we evaluated the combination of losartan plus ivermectin as adjuvant drugs for prophylaxis for serious events among patients with active neoplasia who are highly susceptible to COVID-19 complications.

Methods

Patients and Procedures

Patients were eligible if they were 18 years or older and had an Eastern Cooperative Oncology Group (ECOG) performance status scale score of 0-2, biopsy-proven diagnosis of active cancer (solid or haematologic disease) and confirmed diagnosis of COVID-19 by positive PCR test or positive antigen test and/or by the presence of flu-like symptoms associated with typical radiological findings on CT scan. The exclusion criteria included current use of ACE inhibitors or ARA2s, patients who presented with severe conditions at the time of diagnosis requiring intensive care unit (ICU) admission, prior reaction, or intolerance to an ARA/ACE inhibitor and ivermectin, blood pressure less than 110/70 mmHg at presentation, serum potassium level greater than 5.0 mEq/L, pregnancy or breastfeeding, and patients who were currently enrolled in another research protocol.

After a confirmed diagnosis of COVID-19, patients were randomized 1:1 using REDCap software v9.1.0 (Vanderbilt University, Nashville-TN, USA). Patients allocated to the interventional arm received a single dose of 12 mg of ivermectin on Day 1, followed by 15 consecutive days of losartan 50 mg once a day, whereas patients in the control arm received a single dose of placebo-ivermectin or losartan-placebo on Day 1 and 15 consecutive days of placebo once a day. Patients were followed weekly, and on Days 14 and 21, they underwent physical examinations and blood tests to evaluate any adverse events regarding hepatic or renal function. If any adverse events were observed, the treatment was stopped. Patients who needed to be admitted to the ICU, died or needed mechanical ventilation were defined as having reached the primary endpoint, and treatment was also stopped.

Outcomes

The primary endpoint was the incidence of severe complications due to COVID-19 infection, defined as the need for intensive care unit (ICU) admission, the need for mechanical ventilation (MV), or death. Secondary endpoints included adherence, which was measured by patients' answers to questions regarding pill count after return of the pill container, and safety of the combined drug therapy.

Trial Oversight

An external, independent data monitoring committee periodically assessed safety and efficacy. The trial protocol and all amendments were approved by the ethics committee - *Comissão Nacional de Ética em Pesquisa (CONEP)*. All patients provided written informed consent before enrolment. All the authors attest that the trial was conducted in accordance

with the protocol and its amendments and with the standards of good clinical practice. The ClinicalTrials.gov registration number of this study is NCT04447235. The planned recruitment period was 2 years between July 2020 and June 2022. A preplanned interim analysis to evaluate the safety of the treatment arm was performed after one-third of the patients (58) were enrolled, and if up to 3 severe adverse events (SAEs) related to the experimental arm were observed, the trial would be permanently suspended. The safety analyses were performed in August 2021, and although 3 SAEs were observed, none of them were associated with the experimental drugs, and local and independent committees allowed trial enrolment continuation.

Statistical Analysis

Based on a previous study (Liang et al.), we estimated that 50% of the cancer patients who required hospitalization due to COVID-19 would experience serious events. In the experimental arm, we estimated an improvement, with a reduction of serious events among hospitalized patients to 15%. Considering that approximately 25% of the overall cancer patients would require hospitalization due to COVID-19, these would translate into a proportion of 12.5% (0.5 x 0.25) of serious events in the control arm (placebo) in the overall cancer population and 3.75% (0.15 x 0.25) in the experimental arm (ivermectin and losartan).

With a power of 80% and an alpha one-tailed error of 10%, 176 patients (88 patients in each arm) were needed to demonstrate the estimated differences between the arms (calculated considering the comparison of two independent proportions by Chi-squared test in the Stata software version 15.1).

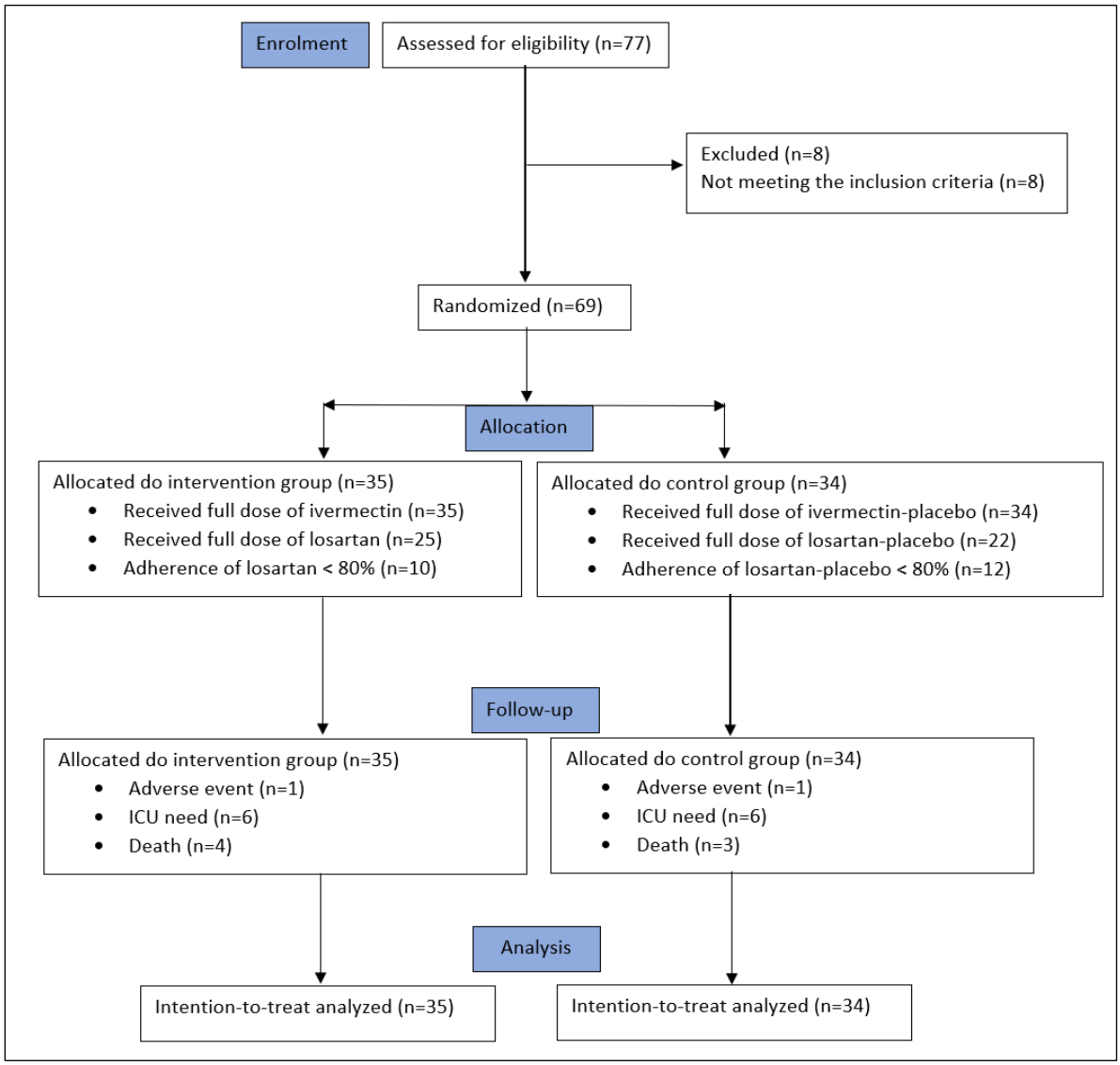
Descriptive statistics were used to summarize the characteristics of the study population. Continuous variables are presented as median and extreme values. Categorical variables are presented as absolute and relative values.

To compare the categorical variables between the groups, the Chi-squared or Fisher's exact test were used. For comparison of continuous variables between groups, Student's t test or the Mann–Whitney U test were used, depending on the distribution of the variable. Efficacy analyses were calculated for the intention-to-treat population. P values below 0.05 were considered statistically significant. Statistical analyses were carried out with the Stata program (StataCorp, Texas, USA).

Results

From July 2020 through June 2022, a total of 77 patients were screened, and 69 patients were randomized. After randomization, 35 patients were assigned to the losartan + ivermectin arm, and 34 patients were assigned to the placebo arm. After the publication of well-designed randomized phase 2/3 trials that demonstrated the inefficacy of ivermectin and losartan separately as COVID-19 treatment, the authors and local institution research committee decided to run an unplanned futility analysis, and the trial was permanently closed. With 69 patients randomized, the study would have a power of 51.6% to detect the estimated difference in the primary endpoint of severe complications. **Figure 1** shows the study CONSORT flow diagram.

Figure 1. CONSORT diagram of the trial.



Patient characteristics

Baseline demographic and disease characteristics were well balanced between the two groups and are shown in **Table 1.** The median age was 50 years; one-third of the patients had breast cancer, and 13% had haematological malignancies. Fifty-nine percent (n=41/69) of the patients had metastatic disease and were receiving active systemic treatment, while only 16% (n=11/69) were receiving systemic treatment in a curative setting. Seventy-seven percent (27/35) of the patients in the experimental arm were not vaccinated, and 5.7% (2/35) received the full 3-dose schedule. Similarly, 73.5% (25/34) of the patients who were allocated to the placebo arm were unvaccinated, and one patient (2.9%) was fully vaccinated. No difference in vaccination status was observed between the arms (*p=0.247*).

Additional treatment for COVID-19 was offered to 37.7% (26/69) of the trial patients, and no difference was observed between the experimental and placebo arms (*p=0.621*). Antibiotics, steroids, and low-molecular-weight heparin were the most common treatments (see **Table S1**).

Table 1. Baseline patient characteristics

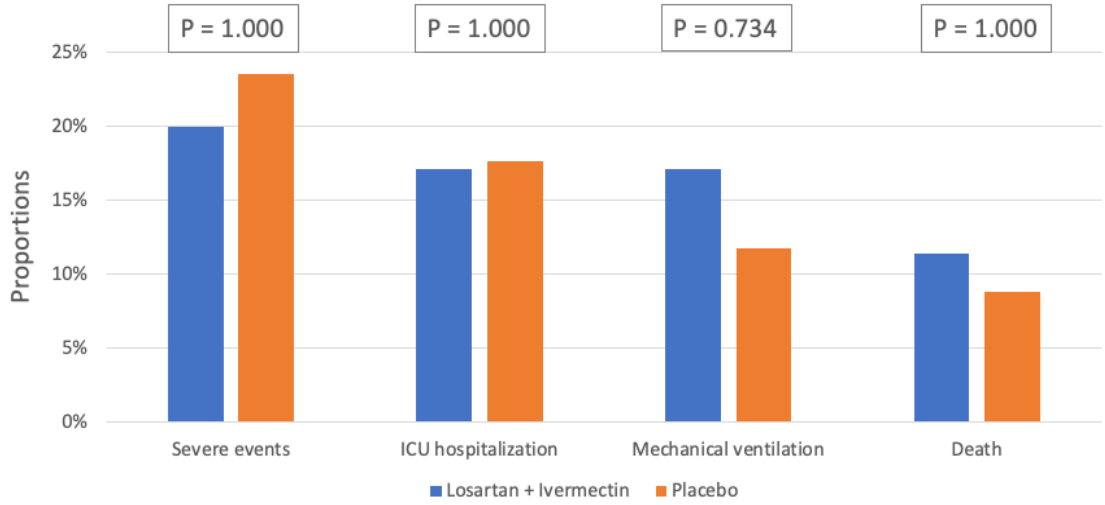
	Losartan + ivermectin (N = 35)	Placebo (N = 34)	*p*
Age, years – median (range)	50 (33–84)	49 (27–74)	0.717 [a]
Cancer type – N (%)			0.266 [b]
Head and neck	0 (0)	3 (8.8)	
Gastrointestinal	9 (25.7)	6 (17.6)	
Lung	2 (5.7)	2 (5.9)	
Soft tissue	0 (0)	4 (11.8)	
Skin	0 (0)	0 (0)	
Breast	12 (34.3)	10 (29.4)	
Gynaecological	4 (11.4)	2 (5.9)	
Urinary tract	4 (11.4)	2 (5.9)	
Central nervous system	0 (0)	0 (0)	
Haematological malignancies	4 (11.4)	5 (14.7)	
ECOG – N (%)			0.537 [b]
0	7 (20)	10 (29.4)	
1	20 (57.1)	16 (47.1)	
2	7 (20)	5 (14.7)	
Not available	1 (2.8)	3 (8.8)	
Disease status – N (%)			0.845 [b]
Initial disease with curative treatment	6 (17.1)	5 (14.7)	
Metastatic disease with active systemic treatment	20 (57.1)	21 (61.7)	
Metastatic disease with best supportive care	1 (2.8)	1 (2.9)	
Metastatic disease without systemic treatment	6 (17.1)	7 (20.6)	
Not available	2 (5.7)	0 (0)	
Previous comorbidities other than cancer – N (%)			0.159 [b]
Any	19 (54.3%)	11 (32.3%)	
Hypertension	7 (20)	2 (5.9)	
Diabetes	4 (14.3)	7 (20.6)	
COPD	1 (2.8)	1 (4)	
Obesity	5 (14.3)	2 (5.9)	
Cardiovascular disease	1 (2.8)	3 (8.8)	
D-dimer – median (range)	1294 (538–103367)	1054 (287–13811)	0.133 [c]
Time from diagnosis to study randomization- median (range)	3 (1–5)	2 (1–6)	0.271 [c]
COVID-19 diagnosis			0.084 [b]
Positive PCR	35 (100)	30 (88.2)	
Negative PCR but symptoms plus typical CT changes	0	4 (11.8)	
Vaccination status			0.247 [b]
3 doses	2 (5.7)	1 (2.9)	
2 doses	1 (2.8)	5 (14.7)	
1 dose	0	1 (2.9)	
None	27 (77.2)	25 (73.5)	
No data	5 (14.3)	2 (5.9)	

[a] Student's t test; [b] Fisher's exact test; [c] Mann-Whitney test

Efficacy

The use of losartan and ivermectin did not improve COVID-19 outcomes compared to placebo (**Figure 2**). A total of 15 severe events occurred in the trial population. Seven patients in the losartan + ivermectin arm (20%) presented severe COVID-19 outcomes versus 8 patients (23.5%) in the placebo arm (*p=1.000*). No difference was observed in the need for ICU admission (17.1% in the experimental arm versus 17.6% in the placebo arm; *p=1.000*) or the need for mechanical ventilation due to respiratory failure (17.1% in the experimental arm versus 11.8% in the placebo arm; *p=0.734*). Four patients died from COVID-19 complications in the losartan + ivermectin arm, whereas 3 patients died in the placebo arm, and this difference was not statistically significant (11.4% versus 8.8%; *p=1.000*). **Table S2** shows the efficacy results between arms.

Figure 2. Efficacy and COVID-19 outcomes between arms.



P-values calculates using Fisher`s exact test.

Adherence

Patient adherence was verified by manual counting of the number of pills in the returned medicine container, in addition to active questioning during weekly visits. Full single-dose ivermectin adherence was achieved in both arms, while losartan adherence was higher than 80% of the planned scheme among two-thirds of the patients (68.6% in the losartan arm versus 64.7% in the placebo arm). **Table 2** demonstrates patients' adherence to the ivermectin and losartan schemes.

Table 2. Treatment adherence

	Losartan + ivermectin (N = 35)	Placebo (N = 34)	*P*[a]
Ivermectin – N (%)	34 (97.1)	34 (100)	1.0
Losartan (full scheme of 15 days) – N (%)	23 (65.7)	20 (58.8)	0.62
Losartan adherence higher than 80% of the scheme – N (%)	24 (68.6)	22 (64.7)	0.80

[a] Chi-Squared test

Safety

Eight severe adverse events were reported during patient follow-up, but after internal and independent committee evaluations, only one, symptomatic hypotension, was considered possibly related to study treatment, and the remaining 7 events were related to oncological disease progression. Nonsevere adverse events are described in **Table 3.**

Table 3. Adverse events

Non-severe adverse events		
	Losartan + Ivermectin (N = 35)	Placebo (N = 34)
Postural hypotension	4 (11.4)	2 (5.8)
Facial oedema	0 (0)	1 (2.9)
Nausea	2 (5.7)	2 (5.9)
Diarrhoea	0 (0)	1 (2.9)
Increase in AST or ALT levels less than 3x the SLN	1 (2.9)	0 (0)
Increase in bilirubin levels less than 3x the SLN	0 (0)	1 (2.9)
Dizziness	4 (11.4)	1 (2.9)
Rash/itching	1 (2.9)	1 (2.9)
Decrease in creatinine clearance	1 (2.9)	0 (0)
Hyperkalaemia	0 (0)	0 (0)
Severe adverse events		
Permanent increase in bilirubin levels	1 (2.9)	-
Decrease in creatinine clearance less than 30 ml/min	2 (5.7)	1 (2.9)
Permanent increase in potassium levels > 5.5 meq/L	1 (2.8)	-
Syncope due to postural hypotension	-	1 (2.9)*
Severe oncological pain	1 (2.8)	-
Cholecystitis	1 (2.8)	-

*This was the only SAE related to the study medications.

Discussion

Patients with cancer seem to be at higher risk of worse outcomes when diagnosed with SARS-COV-2 infection. Most studies performed prior to mass vaccination demonstrated that patients with haematological malignancies, lung cancer, active cytotoxic treatment and poor performance status are at higher risk of developing severe COVID-19 complications[26-30]. In this cohort of patients with initial mild to moderate SARS-CoV-2 infection and active neoplasia and/or active cytotoxic treatment, the mortality rate was 10.1%, which was higher than that of the general population and in line with most previous data[31]. Grivas et al. showed

that the more active the cancer and the more cytotoxic the combination of anticancer drugs, the greater the likelihood of complications from COVID-19 [32]. Our proportion of patients who presented severe outcomes due to coronavirus infection was higher than 20%.

Overall, the management of COVID-19 infection in cancer patients is similar to that in the general population, and specific anti-COVID-19 drugs are often indicated considering patient risk[33]. Among high-risk patients, nirmatrelvir-ritonavir has been considered the initial treatment for symptomatic outpatients with risk for progression to severe disease after a randomized phase 2/3 trial showed that this antiviral combination reduced the risk of hospitalization or death at 28 days by 89% compared with placebo. However, of the 2246 patients who were considered high risk, only 11 were active cancer patients, and no difference was observed in this small subgroup[33]. Other alternative drugs with activity for high-risk patients with mild to moderate COVID-19, such as remdesivir and molnupiravir, only included a total of 30 and 29 active cancer patients, respectively[34,35].

In this context, our trial has a more representative number of this subgroup of patients who were exposed to potentially active reallocated drugs against COVID-19, such as losartan and ivermectin. However, no difference in severe COVID-19 complications was observed between patients who received losartan plus ivermectin versus those who received placebo. The present results are consistent with findings from previous high-quality data that show that ivermectin is ineffective for mild to moderate COVID-19[36,37]. Reis et al. compared 400 mcg/kg orally once daily for three days within seven days of symptoms to placebo among outpatients with symptomatic COVID-19, and no difference was observed between arms (relative risk, 0.90; 95% Bayesian credible interval, 0.70 to 1.16)[36]. Similarly, a Malaysian open-label randomized trial demonstrated no benefit among 490 patients who received a 5-day course of 400 mcg/kg of ivermectin daily. Of note, cancer patients were also underrepresented in this trial, with a total of only 14 patients with active neoplasms[37].

There is a clear rationale for considering inhibition of the renin-angiotensin-aldosterone system (RAAS) as a therapeutic target, as the binding of the SARS-CoV-2 spike protein to the ACE-2 receptor directly causes an imbalance between ACE-1/ACE-2, decreasing the protective inflammatory effect of ACE-2 and leading to lung injury[38]. Duarte et al. showed promising activity of telmisartan among hospitalized patients, with reduced C-reactive protein levels and decreased ICU admission rates and deaths[17]. Although very intriguing, these findings were not reproduced in another two randomized trials[18,19]. Puskarich et al. evaluated 10-day losartan for mildly symptomatic outpatients, and the drug did not reduce the hospitalization rate or viral load compared to placebo. Of note, the low number of events observed may be related to the low number of high-risk patients, none of them cancer patients, which may have limited the assessment. Losartan was also ineffective for inpatients with COVID-19 who were in serious conditions and even showed detrimental effects on haemodynamic and kidney function[18,19]. Our trial found no evidence of the benefit of losartan in mitigating COVID-19 complications in a mild to moderate high-risk population but also found no harmful effects.

The unexpected low adherence may not have adequately suppressed a dysregulated RAAS.

Vaccination is not proportionally as effective among immunocompromised patients, and both mRNA and non-mRNA COVID-19 vaccines have demonstrated erratic seroconversion among cancer patients[14,39]. Palich et al. showed that after one dose of mRNA vaccine, only half of the cancer patients showed seroconversion of neutralizing antibodies, and those who converted had a median serum antibody level lower than that of noncancer patients (680 versus 315 UA/ml, $p = 0.04$) [44]. Current cytotoxic chemotherapy was the main risk factor for patients who were not seroconverted (OR 4.34, IC 95% 1.67-11.30, $p = 0.003$)[39]. Our trial patients were mostly unvaccinated, and more than 70% were receiving systemic treatment, with no difference between arms. These findings reinforce that we selected a high-risk subpopulation that was mostly not immunized, or that those who were unvaccinated had a lower chance of effective seroconversion.

The strengths of our study are the prospective and randomized design, as well as the drug intervention in a high-risk population that was also poorly fully vaccinated. Additionally, to our knowledge, this is the only study registered on *ClinicalTrials.gov* that evaluates active treatment for COVID-19 exclusively for cancer patients and seems to be the trial with the greatest amount of oncological patient data.

Our trial, however, also presents several limitations. The unicentric design presents the risk of institutional biases. The optimal ivermectin dose is controversial, and our trial used a minimum dose that may not have achieved ivermectin antiviral activity. Finally, the losartan adherence of only 65% of the patients receiving 80% or more of the planned dosage was lower than expected.

Conclusion

Faced with an unprecedented pandemic, mitigating COVID-19 complications has been a priority worldwide. Patients with underlying comorbidities are the main individuals affected, and among them, oncological patients seem to have frequent severe outcomes. In this context, the concept of previously approved drug reallocation, which presents therapeutic biological rationale, becomes appealing.

To date, no drug against COVID-19 has been evaluated well specifically among cancer patients, and more randomized studies should evaluate active treatments for this specific high-risk subgroup.

In this prospective, randomized phase II trial, an early treatment strategy based on the reallocation of losartan and ivermectin did not improve severe COVID-19 outcomes among high-risk cancer patients.

LIST OF ABBREVIATIONS

WHO - World Health Organization
SARS - severe acute respiratory syndrome
ACE-2 - angiotensin-converting enzyme 2
ECOG - Eastern Cooperative Oncology Group
ARA2s - angiotensin II receptor antagonists
ICU - intensive care unit
PCR - polymerase chain reaction
CT - computerized tomography
MV - mechanical ventilation
SAE - severe adverse event
RAAS - renin-angiotensin-aldosterone system

DECLARATIONS

Ethical approval:

This study was approved by the National Commission of Ethics in Research of Brazil (CONEP); all participants signed informed consent before enrolment and consented to the publication of this study.

The authors wish to thank the study participants for their contribution to this research.

Competing interests:

There are no competing interests in this trial.

Conflict of Interest Statement:

The authors declare no conflicts of interest.

Acknowledgement Statement:

We thank Ingrid Barbosa for the management of this study.

We thank Instituto do Cancer do Estado de Sao Paulo for integral funding and institutional support.

Funding Statement:

This study was fully funded by Instituto do Cancer do Estado de Sao Paulo.

Authors' contributions:

P.E. and M.D.P.ED. wrote the main manuscript.
P.E. prepared Figures 1-2.
R.C.B. calculated the statistical data.
All authors reviewed the data and the manuscript.

Availability of Data and Materials:

All data generated or analysed during this study are included in this published article and its supplementary information files.

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