The Oncologist, 2022, **27**, 623–e624
https://doi.org/10.1093/oncolo/oyac004
Advance access publication 16 April 2022
Clinical Trial Results

Safety and Tolerability of Carboplatin and Paclitaxel in Cancer Patients with HIV (AMC-078), an AIDS Malignancy Consortium (AMC) Study

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Abstract

Background: Persons living with human immunodeficiency virus are an underserved population for evidence-based cancer treatment. Paclitaxel and carboplatin (PCb) is an active regimen against a variety of solid tumors, including several seen in excess in patients with HIV infection. We performed a pilot trial to evaluate the safety of full-dose PCb in people living with human immunodeficiency virus and cancer.

Methods: Eligible patients, stratified by concurrent antiretroviral therapy (ART) that included CYP3A4 inhibitors or not, received paclitaxel (175 mg/m^2) in combination with carboplatin (target AUC 6) intravenously every 3 weeks for up to 6 cycles.

Results: Sixteen evaluable patients received 64 cycles of PCb, including 6 patients treated with CYP3A4 inhibiting ART (ritonavir). The adverse event profile was consistent with the known toxicity profile of PCb, with no differences between the 2 strata. There were 4 partial responses (25%, 95% CI: 7%-52%), and overall, CD4+ lymphocyte count was similar after completion of therapy (median: 310/μL) compared with baseline values (median: 389/μL). Pharmacokinetic studies in 6 patients revealed no significant differences in C_{max} or AUC_{inf} for paclitaxel between the 2 cohorts.

Conclusion: Full doses of PCb chemotherapy are tolerable when given concurrently with ART in people living with human immunodeficiency virus with cancer, including patients receiving CYP3A4 inhibitors.

ClinicalTrials.gov Identifier: NCT01249443.

Key words: HIV; paclitaxel; carboplatin; ritonavir; antiretroviral

Lessons Learned

- The event profile and broad clinical activity of full-dose carboplatin and paclitaxel treatment in people living with HIV demonstrated an adverse effect profile consistent with the regimen in immunocompetent patients, no significant change in CD4+ cell counts after therapy, and no opportunistic infections.
- Pharmacokinetic studies in 6 patients stratified use of a potent CYP3A4 inhibitor (ritonavir) use revealed no significant differences in C_{max} or AUC_{inf} for paclitaxel, a CYP3A4 substrate.

Received: 11 December 2021; Accepted: 22 December 2021.
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Discussion

In this prospective study of full-dose paclitaxel and carboplatin (PCb) for advanced cancers in people living with HIV (Table 1), we found an adverse event profile consistent with the regimen in immunocompetent patients, no significant change in CD4+ cell counts after therapy, and no opportunistic infections. A total of 64 cycles of therapy were administered to 16 patients, for a median of 4 cycles per patient; all patients tolerated at least 2 full cycles of therapy. Three of 16 patients (19%) had durable partial responses ranging from 19 to 22 months (including patients with anal cancer, other squamous cell carcinoma, and follicular dendritic cell sarcoma), and 6 additional patients (38%) had disease stabilization. Ten percent of the patients experienced grade 3 or higher toxicities, the most common of which were granulocytopenia (40%), infection (15%), and anemia (15%); primary GCSF support was not permitted.

We found no evidence for pharmacokinetic interaction when ritonavir (potent CYP3A4 inhibitor) given at a "boosting dose" for ART was used in combination with paclitaxel, a substrate for CYP3A4 (Table 3). Of note, the C_{max} was similar regardless of ART regimen, and there was no correlation of exposure with efficacy or tolerability.

Table 1. Patient characteristics

Characteristics	Overall (*N* = 16)	Ritonavir (*N* = 6)	Non-ritonavir (*N* = 10)
Age, years, median (range)	56 (42-70)	53.5 (47-63)	58 (42-70)
Gender			
Male	10	3	7
Female	6	3	3
Race and Ethnicity			
Hispanic	2	0	2
Non-Hispanic/White	2	1	1
Non-Hispanic/Black	12	5	7
Histology			
Non-small cell lung	7	2	5
Anal carcinoma	3	2	1
Other cancers[a]	6	2	4
Baseline CD4+ count median (range)	389 (109-642)	357.5 (109-576)	403 (152-642)
Baseline HIV Viral Load			
Undetectable	13	5	8
Detectable	3	1	2
Vorinostat			
None	14	0	0
400 mg PO BID days 1-5	2	0	2

[a]Other cancers: Ritonavir group (breast cancer, esophageal squamous cell carcinoma); non-ritonavir group (cervical cancer; follicular dendritic cell sarcoma; squamous cell carcinoma of unknown primary site; adenocarcinoma of an unknown primary site).

Author disclosures and references available online.

Trial Information	
Disease	HIV-associated—other; Anal Cancer
Stage of disease/ treatment	Metastatic/advanced
Prior therapy	More than 2 prior regimens
Type of study	Phase I, Pilot
Primary endpoint	Toxicity
Secondary endpoint	Pharmacodynamics
Investigator's analysis	Active and should be pursued further

Additional Details of Endpoints or Study Design

Eligibility Criteria

Eligibility criteria included histologically confirmed metastatic or unresectable malignancy with at least one measurable lesion (by RECIST), known HIV infection (positive ELISA, positive Western blot, or any other federally approved licensed HIV test) and CD4 count >100/μL, age >18 years, ECOG performance status 0-2, normal organ function and electrolytes within 2 weeks of study entry (leukocytes, >3000/μL, neutrophils >1500/μL, platelets, >100 000/μL, total bilirubin within normal institutional limits (WNL), AST(SGOT)/ALT(SGPT) <2.5-fold above the institutional upper limit of normal, serum creatinine WNL or >50 mL/minute/1.73 m^2 for patients with creatinine levels above institutional normal or normal serum magnesium and phosphorus. Exclusion criteria included chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C), persistent grade 2 or higher toxicity from prior cytotoxic therapy, grade 2 or higher neuropathy from other causes, treatment with other investigational agents, known brain metastases, history of hypersensitivity to agents used in the study, uncontrolled intercurrent illness, or pregnant or lactating women.

Antiretroviral Therapy

Patients were evaluated as treated either with ritonavir containing ART or others. Treatment with zidovudine or stavudine was not permitted due to potential for hematological toxicity. Paclitaxel dosing was not modified based on ART due to results from a prior trial of paclitaxel alone in people living with HIV concluding that despite pharmacokinetic differences the therapeutic effects were similar in patients on a CYP3A4 inhibitor-containing ART.[1] However, patients were stratified to ritonavir or non-ritonavir cohorts to adequately capture differences in safety, efficacy, and pharmacokinetics.

Protocol Therapy

Patients received carboplatin (AUC 6 via 30-minute infusion) and paclitaxel (175 mg/m^2 via 1-hour infusion) intravenously every 3 weeks for a maximum of 6 cycles. Cycles were administered if neutrophil count was >1500/μL and platelets >100 000/μL, and once recovered from non-hematologic toxicity. Primary GCSF prophylaxis was not permitted, and toxicities were primarily managed with dose reduction. The original design of the study was a phase I trial evaluating the PCb combination with vorinostat (400 mg, 500 mg, or 600 mg orally on days 1-5 of each chemotherapy cycle); the study design was modified after the accrual of 2 patients who received the first vorinostat dose level (without prohibitive toxicity), due to a decision by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) to suspend further development of vorinostat in solid tumors in NCT/CTEP-sponsored trials following a negative phase III trial of chemotherapy with vorinostat/placebo in non–small cell lung cancer.[2]

Patients were assessed with radiological studies every 2 cycles, and tumor response was assessed by RECIST. NCI Common Terminology Criteria for Adverse Events (CTCAE) were used for grading adverse events (version 4.0).

Pharmacokinetic Sampling and Evaluation

Plasma samples were obtained on cycle 1 day 1 after the first dose of paclitaxel. Paclitaxel concentrations were determined using liquid chromatography with tandem mass spectrometric detection with a lower limit of quantitation of 2 ng/mL.[3] PK variables were calculated by standard noncompartmental methods using Phoenix WinNonlin (version 6.3; Pharsight A Certara Company, Cary, NC) as previously described.[1]

Statistical Analysis

Descriptive statistics were reported as median (range: min-max) for continuous variables and as a frequency for categorical variables. Descriptive statistics were computed for participant characteristics, response, adverse events, and paclitaxel pharmacokinetic variables. A 2-sided exact binomial 95% confidence intervals were calculated for the proportion of participants responding.

Drug Information	
Paclitaxel	
Generic/working name	Paclitaxel
Drug type	CYP3A4 substrate
Dose	175 milligrams (mg) per squared meter (m^2)
Route	IV

Carboplatin	
Generic/working name	carboplatin
Drug type	second-generation platinum compound
Schedule of administration	paclitaxel (175 mg/m^2) in combination with carboplatin (target AUC 6) intravenously every 3 weeks for up to 6 cycles.

Patient Characteristics	
Number of patients, male	10
Number of patients, female	6
Age, years	Median (range): 56 (42-70)
Performance status: ECOG	0—0 1—0 2—0 3—0 Unknown—0

Adverse Events

Table 2 shows data available for all grades, and grades 3 and 4.

Pharmacokinetics/Pharmacodynamics

Pharmacokinetic (PK) Sampling and Evaluation

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Statistical Analysis

Descriptive statistics were reported as median (range: min-max) for continuous variables and as a frequency for categorical variables. Descriptive statistics were computed for participant characteristics, response, adverse events, and paclitaxel pharmacokinetic variables. A 2-sided exact binomial 95% confidence interval were calculated for the proportion of participants responding.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's assessment	Active and should be pursued further

Worldwide, approximately 37 million people are living with human immunodeficiency virus (HIV) infection, the virus that causes the acquired immunodeficiency syndrome (AIDS). HIV testing is recommended as a component of routine medical care, not just for individuals with known risk factors,[4] including patients with cancer.[5] Combination antiretroviral therapy (ART) has led to substantial declines in mortality in individuals living with HIV infection in the US[6] and worldwide[7] and the average life expectancy for people living with HIV infection is approaching that of the general population.[8]

Although the risks of non-Hodgkin's lymphoma and Kaposi's Sarcoma, which are "AIDS-defining cancers," are increased substantially in patients with HIV infection, the overall mortality and incidence of these cancers have declined with ART.[9-11] In sharp contrast, other cancers have increased due to aging of the HIV population and increased (2-fold) rates of tobacco use than the general population.[10,12] These common non-AIDS defining cancers, now accounting for more than one-half of all cancers in people living with HIV,[10] may be broadly categorized as (1) tobacco-associated, such as non–small cell lung cancer[13,14] and head and neck cancer,[15] (2) age-associated cancers, such as cancers of the colon,[16] breast,[17] and prostate,[18-20] and (3) viral-associated cancers, such as hepatocellular cancer and anal cancer.

Recent National Comprehensive Cancer Network (NCCN) guidelines recommend that ART should be continued in individuals with HIV infection and cancer; however, regimens may need to be modified to avoid drug-drug interactions with antineoplastic therapy.[21,22] Despite increased awareness of cancer risk, evidence-based treatment approaches are generally lacking for this population due to historical exclusion from cancer clinical trials, and concern for tolerability of cancer therapies due to general immunosuppression and other biases have resulted in known treatment disparities.[23]

Ritonavir and cobicistat are antiretroviral agents commonly used in the treatment of advanced HIV infection that are strong CYP3A4 inhibitors that may interfere with the metabolism of paclitaxel, a CYP3A4 substrate.[24] Although single-agent paclitaxel is a standard treatment option for advanced Kaposi sarcoma,[25] rare reports of severe paclitaxel toxicity have been described that have been attributed to a potential pharmacokinetic interaction between paclitaxel, a known CYP3A4 substrate, with PIs such as ritonavir.[26,27] A previous study evaluated the pharmacokinetics, adverse events, and efficacy of paclitaxel at a dose of 100 mg/m^2 with ART including protease inhibitors in 27 patients with Kaposi Sarcoma and HIV infection. Paclitaxel exposure as measured by AUC was higher among patients receiving PIs (nelfinavir, indinavir, and other multiple protease inhibitors; 5.5 ± 2.2

μM·h) compared to patients not receiving protease inhibitors (2.9 ± 0.7 μM·h).[1] Based on these considerations, we performed a pilot study to evaluate the safety of carboplatin and paclitaxel (175 mg/m^2), a commonly used chemotherapy regimen for a variety of cancers, in patients with cancer and HIV infection. Secondary objectives included determining the response rate in cancers of the aerodigestive tract, and to determine whether there was any pharmacokinetic interaction between paclitaxel and ritonavir-containing ART.

Results

Patient Population

Sixteen evaluable patients were accrued from 7 AMC sites between August 2011 and January 2016. The characteristics of the 16 evaluable patients are shown in Table 1, including 6 patients receiving ritonavir-containing ART and 10 patients receiving non-ritonavir containing ART. Histology included non–small cell lung cancer in 7 patients, anal carcinoma in 3 patients, and other cancers in 6 patients. The median CD4 count was 389/μL, and 13 had an undetectable HIV viral load.

Treatment Administered

Sixteen patients received 65 cycles of PCb, including 6 patients in the ritonavir cohort who received 24 cycles of therapy (median 4, range 2-6), and 10 patients in the non-ritonavir cohort who received 41 cycles of therapy (median 4, range 2-6 cycles). All patients received at least 2 full cycles of therapy. No dose modification or concomitant GCSF was required for paclitaxel or carboplatin in any patient, although treatment delays were required in 5/24 cycles (21%) in the ritonavir cohort, and 8/41 cycles (20%) in the non-ritonavir cohort. Reasons for discontinuation of protocol therapy included completion of therapy in 5 (31%), disease progression in 5 (31%), adverse events in 4 (25%), and change to alternative therapy in 2 (13%) patients, with similar distribution in ritonavir and non-ritonavir cohorts.

Adverse Events

The worst grade adverse events (of any attribution) observed in any cycle of therapy are summarized in Table 2. The most common adverse events (all grades) were neutropenia (n = 17 events in 8 participants), anemia (n = 13 events in 8 participants), nausea (n = 12 events in 8 participants), peripheral sensory neuropathy (n = 12 events in 7 participants) and fatigue (n = 11 events in 10 participants). No opportunistic infections were observed, although one participant (treated with vorinostat prior to study modification) had a recurrence of herpes zoster.

Effect of Chemotherapy on CD4+ Lymphocyte Count and Viral Load

CD4+ lymphocyte counts were similar after completion of therapy in 12 patients (310 and 353/μL, median and mean) compared with baseline value in 16 patients (389 and 389/μL, median and mean).

Antitumor Response and Survival

Of the 16 patients who were evaluable for response, there were no complete and 4 (25%) partial responses as a best response, 6 (38%) had stable disease, and 6 (38%) had relapse/progression. The duration of partial response was maintained for 1, 19, 22, and 22 months after achieving a partial response. There were 10 deaths all related to cancer; 2 occurred off study and 8 occurred on the study, although off treatment.

Pharmacokinetic Analysis

Pharmacokinetic studies were performed in 6 patients: 2 in the ritonavir cohort, 3 in the non-ritonavir cohort (backbones of raltegravir or rilpivirine), and one not on ART. Due to the small number, the patient not on ART was combined with the non-ritonavir cohort. The other patients had incomplete collection of pharmacokinetic samples and therefore are not reported. Pharmacokinetic variables are listed in Table 3. There was a trend for paclitaxel maximal plasma concentration (C_{max}) and area under the curve (AUC_{inf}) to be elevated in the patients on the ritonavir cohort compared to the patients on the non-ritonavir cohort (C_{max} 6.8 and 17.7 vs 4.7 ± 0.6 μM; AUC_{inf} 50.2 vs. 22.8 ± 8.1 μM·hr). The duration spent at a paclitaxel concentration >0.05 μM (22.7 vs. 23.8 hr) was similar. Patients who experienced more significant adverse events had exposures that were in the range of the patients who did not experience the adverse events.

Discussion

We performed a prospective study of carboplatin and paclitaxel, a commonly used chemotherapy regimen for the treatment of advanced cancer, in patients with HIV infection. We found an adverse event profile consistent with the cytotoxic regimen in immunocompetent patients, no significant change in CD4+ cell counts after therapy, and no opportunistic infections during chemotherapy. A total of 64 cycles of therapy were administered to 16 patients, for a median of 4 cycles per patient; all patients tolerated at least 2 full cycles of therapy. Three of 16 patients (19%) had durable partial responses ranging from 19-22 months (including patients with anal cancer, other squamous cell carcinoma, and follicular dendritic cell sarcoma), and 6 additional patients (38%) had disease stabilization.

Of the commonly used ART, protease inhibitors (PIs) are often an integral component of ART. There are currently 10 commercially available protease inhibitors or approved combinations, including ritonavir. All protease inhibitors are metabolized by enzymes that are part of the cytochrome P450 system; of these, ritonavir has the most potent effects in inhibiting CYP3A4, and is now commonly used to "boost" the concentration of other anti-HIV agents metabolized by this pathway. We found no evidence for pharmacokinetic interaction when ritonavir given at a "boosting dose" was used in combination with paclitaxel, a substrate for CYP3A4, thus confirming our previous results.[1]

We found that 10% of the patients experienced grade 3 or higher toxicities, the most common of which were granulocytopenia (40%), infection (15%), and anemia (15%). Of note, the C_{max} was similar between the PI and non-PI groups. While there is increased total exposure as measured by AUC on the PI arm, it is only in 1 patient. As with our previous study, there was no correlation of exposure with efficacy or tolerability. Furthermore, the higher paclitaxel dose

used in this study (175 mg/m^2)—the dose commonly used in treating a wide variety of non-AIDS defining cancers, with the addition of carboplatin does not appear to alter the pharmacokinetics of paclitaxel, particularly in patients receiving non-ritonavir containing regimens. These findings are important since ritonavir-containing regimens are no longer first-line therapy for HIV disease.[28]

The strengths of the study include its prospective conduct which allowed for systematic and careful documentation of the adverse events and collection of multiple pharmacokinetic endpoints. The study's weaknesses include the small sample size. However, because the patients were followed over time, we were able to capture the adverse events over a larger number of chemotherapy cycles. Related to the small sample size, each pharmacokinetic cohort for the ART regimens (the ritonavir and the non-ritonavir cohorts) had a small number of observations, limiting formal comparisons.

We conclude that full-dose PCb may be administered to people living with HIV and cancer in clinical practice, regardless of ART, with expected broad clinical activity. Routine use of GCSF or empiric dose reductions for presumed risk associated with PCb does not seem to be necessary based on our findings. PCb, albeit administered in a different schedule from this report, has been recently established as a standard of care for the management of advanced anal cancer[29]; our results provide additional confidence in treating patients with HIV infection. PCb is also an important cytotoxic chemotherapy backbone for the addition of targeted therapies (eg, bevacizumab),[30] cancer immunotherapies (eg, pembrolizumab),[31] and their combination (eg, bevacizumab plus atezolizumab).[32] Although not all cytotoxic chemotherapy regimens can be evaluated as rigorously, our observations support standard cancer treatment, and efforts in reducing cancer treatment disparities, for this underserved population.

Acknowledgments

Coordinated by the AIDS Malignancy Consortium (Joseph Sparano, MD, Chair) and supported in part by Public Health Service Grant No. UM1CA121947 and the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services. This research was also supported by the Analytical Pharmacology Core of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (NIH grants P30 CA006973 and UL1TR001079) and the Shared Instrument Grant (S10RR026824). The project described was supported by Grant Number UL1TR001079 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research, and its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCATS or NIH.

Conflict of Interest

Missak Haigentz, Jr.: Jazz Pharmaceuticals, Blueprint Medicines, AstraZeneca, Takeda (SAB); Paige Moore: CorEvitas (E [after work on this study]); Michelle A. Rudek: Celgene Corporation, Cullinan Apollo, RenovoRx, Taiho Pharmaceutical (RF [institutional]); Geminus Therapeutics, LLC (E, OI), GlaxoSmithKline (E [spouse]). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Data Availability

The data underlying this article will be shared at reasonable request to the corresponding author.

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Figures and Tables

Table 2. Adverse events, worst grade in any cycle of therapy, by participants*

Adverse events	Ritonavir-based (*N* = 6)			Non-ritonavir based (*N* = 10)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	N	*n*	*N*	*N*	*n*	*n*
Hematologic						
Anemia	2	1	0	6	2	0
Neutropenia	3	0	1	4	2	2
Lymphopenia	0	0	0	2	0	0
Thrombocytopenia	1	0	0	4	1	0
Febrile Neutropenia	1	1	0	0	0	0
Non-hematologic						
Gastrointestinal						
Nausea	4	1	0	4	1	0
Vomiting	3	1	0	1	1	0
Diarrhea	2	0	0	3	0	0
Colitis	1	1	0	0	0	0
Abdominal pain	4	1	0	0	0	0
Anorexia	1	1	0	0	0	0
Neurologic						
Sensory neuropathy	4	1	0	3	0	0
Pain in extremity	1	0	0	0	0	0
Mucocutaneous						
Mucositis	2	0	0	0	0	0
Metabolic and Laboratory						
Hyperglycemia	1	0	0	2	0	0
Hypoglycemia	1	1	0	0	0	0
Hyperkalemia	1	0	0	1	0	0
Hypokalemia	0	0	0	1	0	0
Hypocalcemia	1	0	0	2	0	0
Hypomagnesemia	1	0	0	2	0	0
Hyponatremia	0	0	0	2	1	0
Hypercalcemia	1	0	1	0	0	0
Abnormal liver function	1	0	0	3	0	0
Abnormal renal function	0	0	0	1	0	0
Cardiopulmonary						
Dyspnea	3	0	0	4	1	0
Cough	3	0	0	2	0	0
Aspiration	1	1	0	0	0	0
Thromboembolism	1	1	0	2	1	0
Visceral arterial ischemia	1	1	0	0	0	0
Constitutional and Other						
Fatigue	6	0	0	4	0	0
Dehydration	1	1	0	1	1	0
Weight loss	2	0	0	1	0	0
Limb edema	1	0	0	1	0	0
Infection[a]	1	0	0	2	1	0
Non-cardiac chest pain	1	1	0	0	0	0

*Includes adverse events observed in at least 1 participant.
[a]Infection associated with normal absolute neutrophil count.

Table 3. Paclitaxel pharmacokinetic variables during cycle 1 (n = 6)

Antiretroviral regimen	*n*	Pharmacokinetic parameters[a]			Time > $C_{0.5\ \mu M}$ (hr)
		C_{max} (μM)	AUC_{inf} (μM·hr)	Cl (L/hr/m^2)	
Ritonavir cohort	2	6.8, 17.7	50.2	4.1	22.7
Non-ritonavir cohort	4	4.7 ± 0.6	22.8 ± 8.1	9.8 ± 3.0	23.8 (22.2-24.8)

[a]Values are reported as the average ± standard deviation (*n*) except for Time > $C_{0.5\ \mu M}$, which is reported as a median (range). The individual data are presented for 2 or fewer patients.
Abbreviations: AUC, area under the concentration–time curve; C_{max}, maximal plasma concentration; Cls, systemic clearance; Time > $C_{0.5\ \mu M}$, time above a concentration of 0.5 μM; NR, not reportable.