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PHASE II STUDIES

A randomized phase 2 trial of the efficacy and safety of a novel topical povidone-iodine formulation for Cancer therapy-associated Paronychia

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Summary

Purpose Cancer therapy-associated paronychia (CAP) is a frequent adverse event associated with cytotoxic and targeted therapies that may impact dosing of anticancer therapies and patient quality of life (QoL). There are currently no evidence-based management strategies or approved treatments for CAP. *Materials and Methods* This was a prospective, multicenter, randomized, double-blind, vehicle-controlled phase 2 study that evaluated the efficacy and safety of 6 to 8 weeks of 1% or 2% povidone-iodine (PVP-I) topical solution versus vehicle-control in adult patients with CAP. Patients were randomized to one of three treatment arms administered twice daily: 1% PVP-I (Cohort A), 2% PVP-I (Cohort B), or vehicle-control (Cohort C). The primary endpoint was a two-grade reduction (or reduction to grade 0 if involved nails were grade 1) on the six-point Paronychia Severity Grading (PSG) scale. Secondary endpoints included safety and the effect on QoL and microbiota. *Results* A total of 102 patients with cancer were randomized to the study. In Cohort A, 83 of 205 (40.5%, $P = 0.6059$) affected nails met the primary endpoint versus Cohort C. In Cohort B, 88 of 167 (52.7%, $P = 0.0063$) affected nails met the primary endpoint versus 64 of 169 (37.9%) in Cohort C. Nineteen of 29 patients (65.5%) in Cohort B reported moderately or very painful nails at baseline that decreased to 15 patients (51.7%) at visit 2 and five patients (17.2%) at visit 3. *Conclusions* Treatment with twice-daily topical 2% PVP-I was safe and resulted in improvement in CAP compared with control. Clinicaltrials.gov identifier: NCT03207906. https://clinicaltrials.gov/ct2/show/NCT03207906

Keywords Paronychia · Quality of life · Anticancer · Toxicity · Povidone-iodine

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Introduction

Cancer therapy-associated paronychia (CAP) is a disorder characterized by acute inflammation of the nail unit caused by the administration of targeted and cytotoxic agents [1–8]. Epidermal Growth Factor Receptor Inhibitors (EGFRI) and taxanes are the most commonly reported causative agents, with incidence rates of 17.2% and 35.7%, respectively [9, 10]. Mitogen-activated protein kinase enzyme (MEK) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, anthracyclines (primarily doxorubicin), and DNA/RNA synthesis inhibitors (eg, capecitabine) can result in CAP in up to 12% of patients [11–14].

CAP has a negative impact on patient quality of life (QoL) and can impact cancer therapy dosing [15]. Nail changes associated with higher morbidity include

periungual erythema, edema, exudate, and suppurative onycholysis [16]. Additionally, the nail may also be affected by periungual or subungual pyogenic granulomas, especially in patients treated with EGFRIs [17]. These changes can cause pain and discomfort, leading to impairment of daily manual activities, deambulation, and even necessitate modification or discontinuation of anticancer treatment [15, 18].

Povidone-iodine (PVP-I) has long been recognized as a broad spectrum, resistance-free biocidal agent. VBP-926 (Veloce BioPharma, LLC, Fort Lauderdale, FL) is a novel PVP-I formulation for topical application to the nail, providing anti-microbial and anti-inflammatory effects. Preliminary anecdotal data obtained from a retrospective review of patients with CAP showed this novel PVP-I formulation to be well tolerated, with encouraging preliminary efficacy [19]. Few clinical trials of potential treatments for cutaneous adverse events (AE) associated with cancer therapy exist, and there are no randomized, controlled trials, or approved treatments for CAP. This is the first randomized phase 2 trial for CAP that is comparing topical PVP-I 1% and 2% nail solution to vehicle-control.

Materials and methods

This was a multicenter, prospective, randomized, double-blind, vehicle-controlled, phase 2 study of adult patients with cancer who developed acute paronychia associated with cancer therapy. The trial was conducted at 14 centers. Cancer therapy categories included EGFRIs, taxanes, MEK inhibitors, and mTOR inhibitors. The duration of the study was 8 weeks and there were three study visits during that timeframe (Day 1; 2 to 4 weeks; 6 to 8 weeks). All study procedures were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to classify three grades of nail changes resulting from cancer therapy. Grade 1 changes were defined as nail fold edema or erythema and disruption of the cuticle. Grade 2 changes were defined as nail unit changes that included nail fold edema or erythema with pain associated with discharge or nail plate separation leading to limitation of instrumental activities of daily living (ADL). Localized intervention was indicated by means of oral intervention. Grade 3 changes were defined as limiting self-care ADL, necessitating surgical intervention or intravenous antibiotics [20]. Furthermore, a Paronychia Severity Grading (PSG) scale with three additional grades was developed to better delineate clinically relevant differences in the disease state and to provide the precision needed for the conduct of rigorous clinical trials evaluating the efficacy of therapeutic agents (Table 1).

Study endpoints

The primary objective of this study was to evaluate the efficacy of twice daily 1% or 2% PVP-I topical solution versus vehicle-control in adult patients with cancer therapy-associated paronychia as evidenced by a two-grade reduction (or reduction to grade 0 if involved nails were grade 1) on the six-point Paronychia Severity Grading (PSG) scale. Secondary objectives assessed the impact on QoL, the antimicrobial effect of PVP-I obtained from baseline bacterial cultures and from nail clippings for fungus identification, and safety.

Eligibility criteria

Eligible patients were men or women, 18 years or older, with acute paronychia developing during anticancer therapy with involvement of at least one nail, and a PSG scale score of one or higher. Current treatments for paronychia at the time of screening were discontinued, and patients agreed not to use any other topical products other than randomized study therapy. Individuals already prescribed antibiotics for any condition, excluding paronychia, continued treatment. Exclusion criteria included patients with paronychia requiring surgical intervention at baseline, history of hypersensitivity to PVP-I, and neutropenia.

Each patient received both verbal and written instructions for proper dosing and study treatment application techniques. Patients were instructed to apply two drops from the bottled nail solution (1% PVP-I, 2% PVP-I, or vehicle-control) using the supplied medicine dropper to each affected nail twice daily. A supplied brush was used to paint the affected areas of the skin around and under the distal nail plate and to the nail plate itself; the

Table 1 Six-point paronychia severity grading scale

Grade 0	No signs or symptoms of paronychia
Grade 1	Erythema of periungual skin
Grade 2	Erythema, edema of periungual skin
Grade 3	Erythema, edema, discharge from periungual skin
Grade 4	Erythema, edema, discharge, periungual granulation tissue
Grade 5	Erythema, edema, discharge, subungual granulation tissue

solution was then allowed to absorb and dry. If a patient experienced dryness or irritation, the investigator was permitted to consider less frequent applications of the solution as required for the symptomatic relief of skin dryness or irritation.

Response assessment

Treatment response was assessed by clinical grading using the morphologic six-point PSG scale (Table 1). The primary efficacy endpoint was defined as a two-grade reduction (or reduction to zero if nails involved were grade 1 at baseline) on the PSG scale. Secondary efficacy endpoints included paronychia QoL responses, microbiologic responses, and safety. For microbiological assessments, a bacterial culture and nail clipping with periodic acid-Schiff (PAS) staining for fungus was obtained from the most severely affected (highest grade) nail of the fingers or toes. Cultures and nail clippings were obtained from the same nail at baseline, first follow-up, and final study visit. The QoL questionnaire used was the HFS-14, a specific quality of life scale developed for patients suffering from Hand–Foot Syndrome, which is readily applicable to paronychia (Fig. 1). Questionnaires were completed at baseline and each subsequent visit [21].

Safety

Safety was evaluated for all treated patients using physical examinations. AE severity, duration, and relationship to study drug were recorded. Cutaneous safety evaluations were recorded by the investigator on a scale of zero (none) to four (very severe) and included erythema, edema, vesiculation, bullae, and necrosis. Details of AEs and physical examinations throughout the study duration were collected and summarized and reviewed for potential significance and clinical importance.

Randomization and blinding

Prior to the start of the study, a randomization list was generated. At the baseline visit, study personnel used an Interactive Web Response System (IWRS) to allocate unique kit numbers to eligible patients. Participants were assigned to receive assigned treatment 1% PVP-I topical solution, 2% PVP-I topical solution, or vehicle-control in 1:1:1 ratio using the IWRS system. The study design was double-blind; the topical medication was packaged in identically labeled containers regardless of treatment group assignment, medication was dispensed by a third party, and the randomization list was locked, with access restricted to designated personnel.

Statistical methods

All data remained anonymized to protect the identities of patients involved in the research. The demographic data were analyzed using descriptive statistical methods for each of the three treatment arms. For continuous variables, number of non-missing observations (n), mean, standard deviation (SD), median, maximum and minimum (range) were calculated. For categorical data, the number of patients (*N*) out of the total number of exposed patients, along with percentages, were calculated for each category of variable. All statistical analyses were performed using The SAS System software, version 9.4 or later (©2000 SAS Institute Inc., Cary, North Carolina). All statistical tests were carried out as two-sided on a 5% level of significance, unless otherwise stated. In particular, all confidence intervals were 95% intervals. The primary efficacy analysis was performed on individual nails and for each individual study patient; comparisons were made using the Chi-square/Fisher's exact test for the primary efficacy variable for each of the active treatment groups versus the vehicle-control group. Microbiologic response was defined as a negative culture or PAS stain where a positive culture or PAS stain had been present. The paronychia QoL score was analyzed using a summed score calculated from responses provided by the patients.

Results

Demographics and clinical characteristics

After screening, 102 patients from 14 sites were randomized, with 35, 34, and 33 patients randomized into Cohort A, Cohort B, and Cohort C, respectively (Fig. 2). The rate of study completion was high ($N = 85$): 77.1% in Cohort A, 85.3% in Cohort B, and 87.9% in Cohort C. No patients discontinued early due to related AEs, and the most common reason for early study discontinuation was loss to follow-up (8.8% across all groups). Baseline demographics and clinical characteristics were similar between groups. More than half of patients (60.8%) were female, with a mean age of 56 years. Median duration of paronychia before inclusion in the trial was zero days for Cohorts A, B, and C; most patients were enrolled the day of diagnosis by the treating oncologist. A total of 205 nails with paronychia were included in Cohort A, 167 were included in Cohort B, and 169 were included in Cohort C (Table 2).

Fig. 1 Paronychia quality of life questionnaire

1. Specify the area affected by your paronychia:
_____ 1 Finger nails _____2 Toe nails _____ 3 Both

2. Would you say your paronychia tends to be:
_____ 1 Very painful _____ 2 Moderately painful _____ 3 Not painful

Please respond to the following statements as spontaneously as possible. There is no right or wrong answer, just whatever corresponds to what you experience on a daily basis

1. I find it hard to turn the key in my door because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

2. I find it hard to prepare my meals because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

3. I have difficulty performing everyday actions because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

4. I have difficulty washing myself, putting on makeup (or shaving) because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

5. I find it hard to drive my car because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never _____ 4 Not relevant to me

6. I find it hard to put on my stockings/tights /socks because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

7. I take longer than usual to get dressed because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

8. I have difficulty putting on my shoes because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

9. It is hard for me to stand because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

10. I have difficulty walking, even over quite short distances, because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

11. I tend to stay seated or lying down because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

12. I find it hard to fall asleep because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____3 No, never

13. My work is suffering because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____3 No, never _____ 4 Not relevant to me

14. My relationships with others are less amicable because of my paronychia:
_____ 1 Yes, always _____ 2 Yes, from time to time _____ 3 No, never

Indicate the level of your pain by placing a vertical stroke between
"No pain" and "Maximum pain imaginable".

No pain I----------I Maximum pain imaginable
0 1 2 3 4 5 6 7 8 9 10

Discontinuation rates of medical antitumor therapy before completion of the study were low among cohorts. Of the four patients in Cohort A who discontinued antitumor therapy, study drug was administered for a mean of 26 days after discontinuation, involving 30 nails total, with 15/30 (50.0%) nails reaching the primary endpoint. Of the five patients in Cohort B who discontinued antitumor therapy, study drug was administered for a mean of 11 days after discontinuation, involving 21 nails total, with 18/21 (85.7%) nails reaching primary endpoint. For the five patients in Cohort C who discontinued antitumor therapy, drug was administered for a mean of 24 days after discontinuation, involving nails total, with 14/29 (48.3%) nails reaching primary endpoint.

There were three patients in Cohort A and four patients each in Cohort B and Cohort C taking antibiotics at the baseline visit for a condition other than paronychia. Of the nails treated in these patients, 4/8 (50%), 2/24 (8.3%) and 13/38 (34.2%) met the primary endpoint of a two-grade reduction (or reduction to grade 0 if involved nails were grade 1) on the PSG scale.

Efficacy

The primary efficacy endpoint was defined as a two-grade reduction (or reduction to grade 0 if involved nails were grade 1) of the scaled score on the six-point PSG scale for each nail. A total of 541 nails were

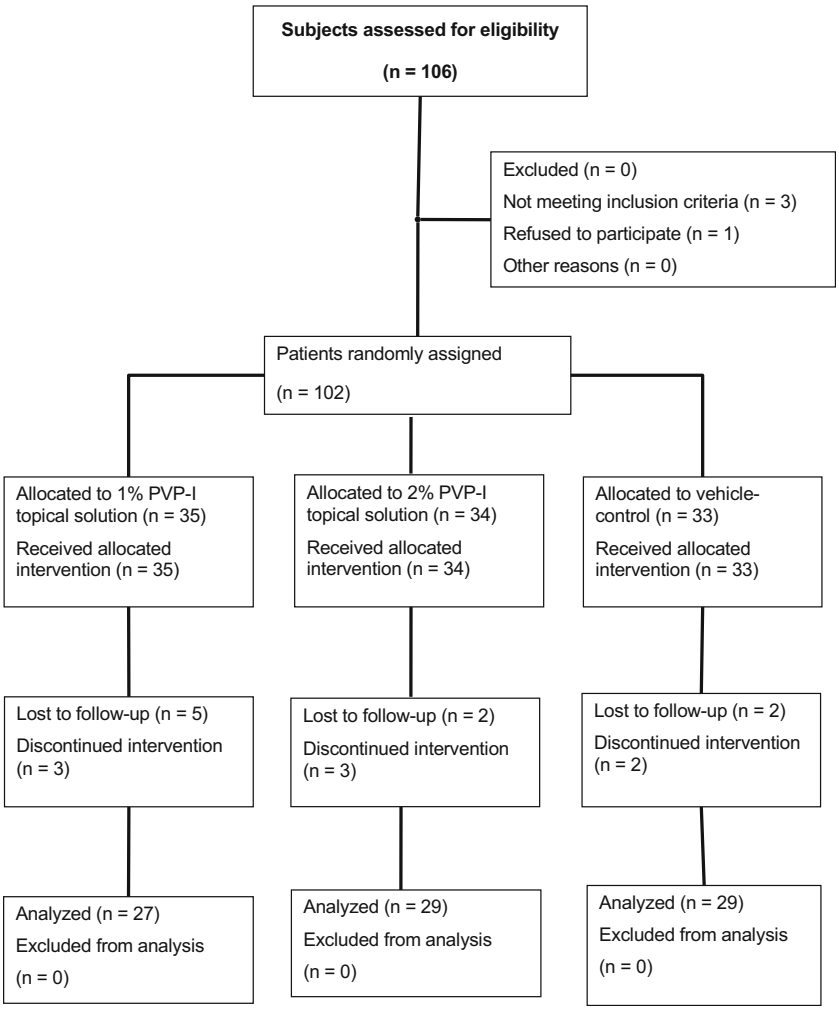

Fig. 2 CONSORT Diagram

included in the trial for analysis. In Cohort A, 83 of 205 (40.5%, $P = 0.6059$) affected nails met the primary endpoint versus Cohort C (Fig. 3). In Cohort B, 88 of 167 (52.7%, $P = 0.0063$) affected nails met the primary endpoint (Fig. 4) versus 64 of 169 (37.9%) affected nails in Cohort C. For Cohort A, 71 of 148 (48%) nails in patients treated with taxanes, two of 13 (15.4%) nails in patients treated with MEK/mTOR inhibitors, one of four (25%) nails in patients treated with EGFRIs, and for combination therapy nine of 40 (22.5%) nails reached the primary endpoint. For Cohort B, 57 of 110 (51.8%) nails in patients treated with taxanes, one of one (100%) nail in patients treated with MEK/mTOR inhibitors, 14 of 15 (93.3%) nails in patients treated with EGFRIs, and for combination therapy 21 of 41 (51.2%) nails reached the primary endpoint. For Cohort C, 45 of 129 (34.9%) nails in patients treated with taxanes, no nails treated with EGFRIs, and for combination therapy 19 of 38 (50.0%) nails reached primary endpoint.

Quality of life

Patients were asked to complete the QoL questionnaire at each visit (Fig. 1). An overall pain assessment using patient-reported pain level was compared with baseline at each subsequent visit. Of patients in Cohort A, 20 of 27 (74.1%), 16 of 27 (59.3%), and 10 of 27 (37.0%) reported moderately or very painful nails at baseline, visit 2, and visit 3, respectively. Of patients in Cohort B, 19 of 29 (65.5%), 15 of 29 (51.7%), and 5 of 29 (17.2%) reported moderately or very painful nails at baseline, visit 2, and visit 3, respectively. Of patients in Cohort C, 21 of 29 (72.4%), 16 of 29 (55.2%), and 10 of 29 (34.5%) reported moderately or very painful nails at baseline, visit 2, and visit 3, respectively. At visit 3, pain-free nails were reported in 17 of 27 (63.0%), 24 of 29 (82.8%), and 19 of 29 (65.5%) patients in Cohorts A, B, and C, respectively (Fig. 5). The study was not powered to detect any statistically significant difference between treatment groups for QoL assessments.

Table 2 Patient demographics

	1% PVP-I (*N* = 35)	2% PVP-I (*N* = 34)	Vehicle-Control (*N* = 33)	Overall (*N* = 102)
Age, years				
Mean	55.8	58.8	52.2	55.6
Gender, n (%)				
Male	12 (34.3%)	14 (41.2%)	14 (42.4%)	40 (39.2%)
Female	23 (65.7%)	20 (58.8%)	19 (57.6%)	62 (60.8%)
Primary Cancer, n (%)				
Breast	14 (40.0%)	12 (35.2%)	14 (42.4%)	40 (39.2%)
Colon	2 (5.7%)	3 (8.8%)	2 (6.1%)	7 (6.9%)
Gynecologic	2 (5.7%)	1 (2.9%)	3 (9.1%)	6 (5.9%)
Lung	9 (25.7%)	9 (26.5%)	2 (6.1%)	20 (19.6%)
Lymph	0 (0.0%)	1 (2.9%)	1 (3.0%)	2 (2.0%)
Oropharynx	4 (11.4%)	3 (8.8%)	2 (6.1%)	9 (8.8%)
Pancreas	1 (2.9%)	2 (5.9%)	1 (3.0%)	4 (3.9%)
Prostate	0 (0.0%)	1 (2.9%)	3 (9.1%)	4 (3.9%)
Rectal	1 (2.9%)	1 (2.9%)	1 (3.0%)	3 (2.9%)
Other	2 (5.7%)	1 (2.9%)	4 (12.1%)	7 (6.9%)
ECOG Performance Status, n (%)				
0	4 (11.4%)	4 (11.8%)	5 (15.2%)	13 (12.7%)
1	23 (65.7%)	21 (61.8%)	18 (54.5%)	62 (60.8%)
2	8 (22.9%)	9 (26.5%)	10 (30.3%)	27 (26.5%)
CTCAE Grade of Nails with Paronychia at Baseline, n (%)				
Grade 1	55 (26.8%)	53 (35.6%)	42 (24.9%)	150 (27.8%)
Grade 2	136 (66.3%)	97 (58%)	96 (56.8%)	328 (60.6%)
Grade 3	14 (6.8%)	18 (10.8%)	31 (18.3%)	63 (11.6%)
Tumor therapy, Number of nails				
Taxanes	148	110	129	387
MEK/mTOR inhibitors	13	1	0	14
EGFRIs	4	15	2	21
Combination of classes	40	41	38	119
Median Duration Prior Medical Antitumor Treatment, Days	83	161	103	103
Adherence to treatment > 80%, n (%)	25/27 (92.6%)	26/27 (96.3%)	29/29 (100%)	80/83 (96.4%)

ECOG Eastern cooperative oncology group. *CTCAE* Common terminology criteria for adverse events, *MEK* Mitogen-activated protein kinase, mTOR Mammalian target of rapamycin, EGFRI Epidermal growth factor receptor inhibitor

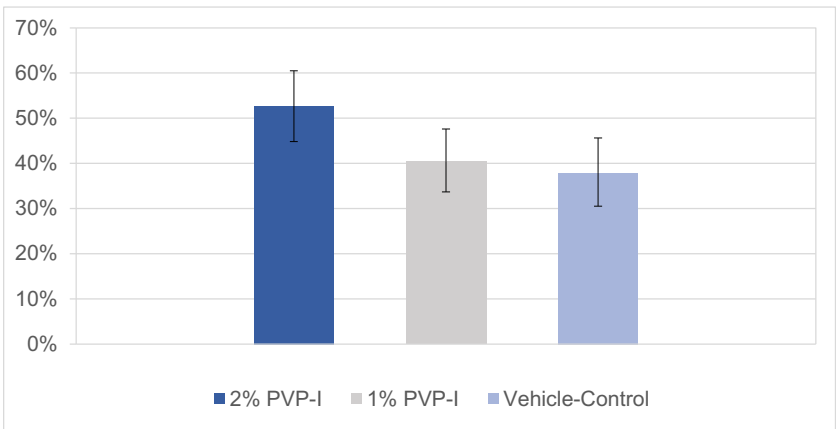

Fig. 3 Percentage of nails with a two-grade reduction (or reduction to zero if nails involved are only grade 1) in each treatment group. (*P* = 0.0063 [95% CI] 2% PVP-I vs. vehicle-control)

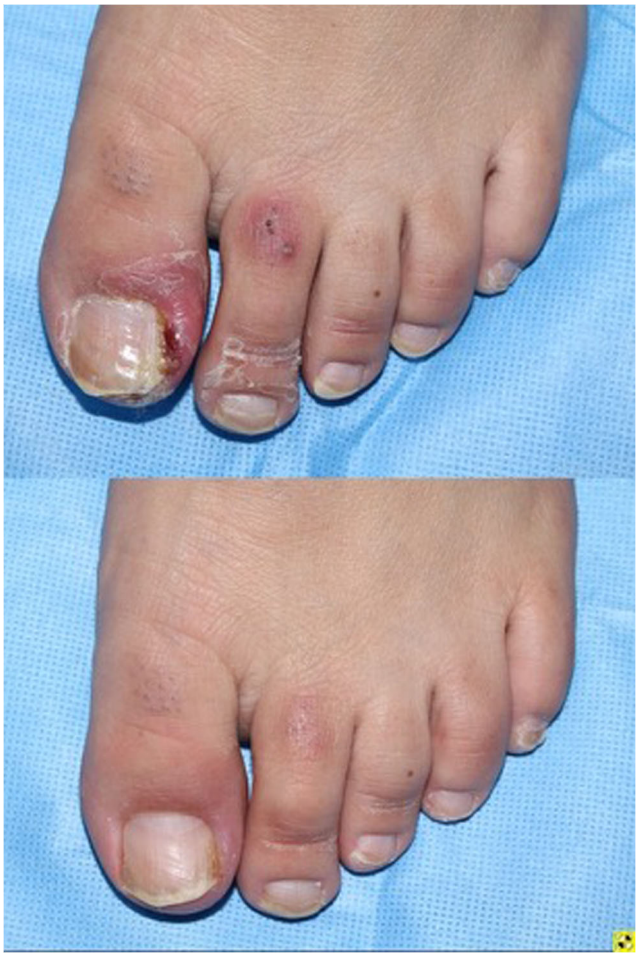

Fig. 4 Patient in Cohort B at baseline (top) and visit 3 (bottom) 6–8 weeks later with a two-grade reduction on the Paronychia Severity Scale

Microbiologic response

There were 47 patients across all treatment groups with a positive bacterial culture at baseline, and 15 patients across all treatment groups with a positive PAS stain at baseline. Of patients in Cohort A, six of 12 (50%) with a positive bacterial culture achieved cure and one of five (20%) patients with positive fungal culture achieved cure at end of study. Of patients in Cohort B, 11 of 16 (68.8%) patients with a positive bacterial culture achieved cure and two of five (40%) patients with positive fungal culture achieved cure at end of study. In Cohort C, 12 of 17 (63.2%) patients with a positive bacterial culture achieved cure and one of five (20%) patients with positive fungal culture achieved cure at end of study. Similar to the analysis of QoL, this study was not powered to detect any statistically significant difference between treatment groups for microbiologic assessments.

Safety

There were few treatment-related AEs, and all were grade 1 (Table 3). Of patients in Cohort A, two of 35 (5.7%) had grade 1 (mild) reactions. For Cohort B, three of 34 (8.8%), and for Cohort C, one of 33 (3.0%) had grade 1 (mild) reactions. No patients required dose reductions, interventions, or discontinued the trial due to treatment-related AEs.

Discussion

CAP is a frequent adverse event that negatively affects patient functioning and dosing of antineoplastic agents, and only anecdotal data support current treatment recommendations. Current management strategies aim to minimize periungual trauma and inflammation, preventing secondary infection, and eliminating excessive granulation tissue, although there is no standard of care and no agent currently approved for treatment. Recommendations for minimizing CAP include wearing comfortable shoes, trimming nails and avoiding aggressive manicuring, and wearing gloves while performing household chores. Topical corticosteroids, anti-inflammatory

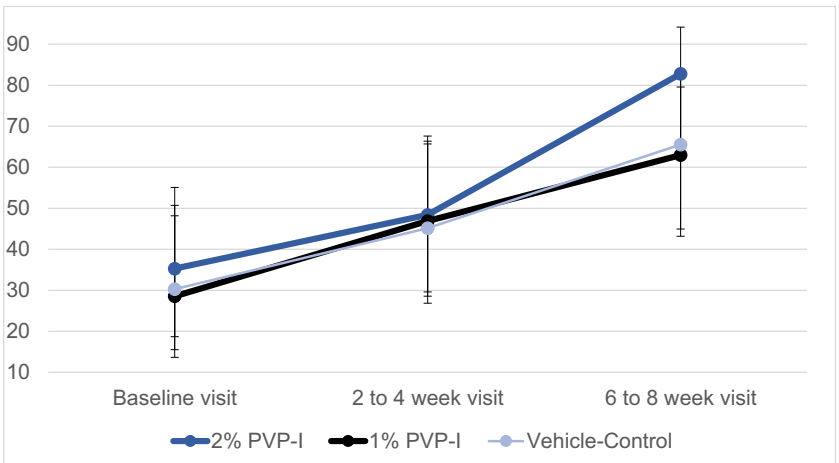

Fig. 5 Percentage of pain free nails at baseline, visit 2 (2–4 weeks) and visit 3 (6–8 weeks). ($P = 0.1338$ [95% CI] 2% PVP-I vs. control at visit 3)

Table 3 Adverse events

	1% PVP-I ($N = 35$)		2% PVP-I ($N = 34$)		Vehicle-Control ($N = 33$)		Overall ($N = 102$)	
	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Total	8	6 (17.1%)	9	7 (20.6%)	10	7 (21.2%)	27	20 (19.6%)
Gastrointestinal disorders	0	0 (0.0%)	1	1 (2.9%)	1	1 (3.0%)	2	2 (2.0%)
Abdominal pain	0	0 (0.0%)	1	1 (2.9%)	1	1 (3.0%)	2	2 (2.0%)
Administration site conditions	3	3 (8.6%)	2	2 (5.9%)	2	2 (6.1%)	7	7 (6.9%)
Application site irritation	0	0 (0.0%)	1	1 (2.9%)	0	0 (0.0%)	1	1 (1.0%)
Application site pain	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.0%)	1	1 (1.0%)
Asthenia	1	1 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.0%)
Peripheral edema	1	1 (2.9%)	0	0 (0.0%)	1	1 (3.0%)	2	2 (2.0%)
Xerosis	1	1 (2.9%)	1	1 (2.9%)	0	0 (0.0%)	2	2 (2.0%)
Infections	1	1 (2.9%)	1	1 (2.9%)	1	1 (3.0%)	3	3 (2.9%)
Cystitis	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.0%)	1	1 (1.0%)
Pneumonia	0	0 (0.0%)	1	1 (2.9%)	0	0 (0.0%)	1	1 (1.0%)
Urinary tract infection	1	1 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.0%)
Injury	1	1 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.0%)
Lumbar vertebral fracture	1	1 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.0%)
Investigations	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.0%)	1	1 (1.0%)
Weight decreased	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.0%)	1	1 (1.0%)
Musculoskeletal disorders	0	0 (0.0%)	0	0 (0.0%)	2	1 (3.0%)	2	1 (1.0%)
Groin pain	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.0%)	1	1 (1.0%)
Musculoskeletal chest pain	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.0%)	1	1 (1.0%)
Nervous system disorders	1	1 (2.9%)	1	1 (2.9%)	0	0 (0.0%)	2	2 (2.0%)
Dysgeusia	0	0 (0.0%)	1	1 (2.9%)	0	0 (0.0%)	1	1 (1.0%)
Peripheral sensory neuropathy	1	1 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.0%)
Respiratory disorders	0	0 (0.0%)	1	1 (2.9%)	0	0 (0.0%)	1	1 (1.0%)
Throat irritation	0	0 (0.0%)	1	1 (2.9%)	0	0 (0.0%)	1	1 (1.0%)
Skin disorders	2	2 (5.7%)	3	3 (8.8%)	3	3 (9.1%)	8	8 (7.8%)
Dermatitis	0	0 (0.0%)	0	0 (0.0%)	1	1 (3.0%)	1	1 (1.0%)
Erythema	1	1 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.0%)
Onychomadesis	0	0 (0.0%)	1	1 (2.9%)	1	1 (3.0%)	2	2 (2.0%)
Pain of skin	0	0 (0.0%)	2	2 (5.9%)	1	1 (3.0%)	3	3 (2.9%)
Rash	1	1 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (1.0%)

doses of tetracycline, and antimicrobial soaks to prevent secondary infection are also recommended, as are topical or oral antibiotic/antimycotic agents to treat secondary infection [22–28]. Additionally, electrocautery, silver nitrate, nail avulsion, and topical timolol can eliminate excessive granulation tissue [7, 29, 30]. In addition to our published case series showing efficacy with a topical PVP-I formulation, platelet-rich plasma has also been reported as beneficial [19, 31]. Recognizing paronychia is important considering the neutropenia that often occurs during cancer therapy, and sepsis has been reported as originating from bacterial and fungal (*Fusarium sp.*) infection of the nail unit [32, 33]. No correlation has been shown between the severity of paronychia and drug concentration at the site of paronychia [34].

This trial demonstrated statistical ($P = 0.0063$) and clinical significance for the primary efficacy outcome measurement of a two-grade reduction (or reduction to grade 0 if involved nails were grade 1) on the six-point PSG scale. A dose effect was shown with 1% versus 2% PVP-I topical solution. Observed rates of discontinuation of medical antitumor therapy were low and evenly distributed between treatment groups. Further, nail changes often persist after drug withdrawal and paronychia has been reported to require several months to achieve healing of the physical findings, exclusive of pain [35, 36]. Patients in Cohorts A, B, and C who discontinued medical antitumor treatment did so on average 11 to 26 days before completing study drug administration, hence it is unlikely that discontinuation of antitumor therapy affected

efficacy outcomes for PVP-I. Enrollment of patients taking systemic antibiotics was not a confounding factor; these patients in Cohorts B and C reached the primary endpoint at a lower incidence than those not taking antibiotics.

For secondary efficacy endpoints, QoL assessments showed that patients administered 2% PVP-I reported a greater reduction in pain across study visits and higher incidence of pain-free nails at the end of study. Pain also improved in the 1% PVP-I and vehicle-control group over time, which may be due to the inherent moisturizing qualities and the physical act of brushing the nail unit associated with the application of the drug or vehicle control.

Microbiology results were impacted by both the small sample size and the vehicle-control converting positive bacterial cultures and PAS stains to negative. The positive baseline cultures were likely not representative of true infection. Future trials should focus upon culturing only nails with frank purulence. PAS results were also confounded by pre-existing onychomycosis in most patients; converting to a negative PAS in a 6 to 8-week time frame is unlikely. Nail grade improvement measured by the primary endpoint and clearance of bacterial or fungal infection are independent variables.

This was the first study to utilize the morphologic six-point PSG scale adapted from the CTCAE in the assessment of treatment response. Overlap between the observed grades, depending on observer experience with the grading criteria, is possible. Furthermore, most patients were categorized into the most inclusive grade 2 (~60% of nails in this study were CTCAE Grade 2). This assessment tool has not been formally validated; interestingly, a novel grading system for paronychia related to oncologic treatments that shares many attributes with the PSG scale developed for this trial was recently published [37]. The current study shows that the six-point PSG can be utilized in the assessment of a treatment response for a therapy specifically targeting cancer therapy-associated paronychia.

In conclusion, CAP is a well-documented, painful, potentially treatment-altering adverse event of numerous chemotherapies. Current treatment modalities for CAP are limited to anecdotal options, with no currently approved therapies. Treatment with 2% PVP-I topical solution showed clinically and statistically superior efficacy compared with vehicle control, and improved QoL with an excellent safety profile.

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Compliance with ethical standards

Conflict of interest K. Capriotti owns equity and is an employee of Veloce BioPharma. M. Anadkat has received honoraria for consulting and/or speaking engagements in the past from Adgero, Astra Zeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Biogen, Eli Lilly, Genentech, ImClone, Therakos, Xoma, and Eisai and has also served as a Principal Investigator for Biogen, Veloce BioPharma, Xoma, Hana Biosciences, and InflamRx. J. Choi declares that she has no conflict of interest. B. Kaffenberger is an Investigator for Biogen, Celgene, Eli Lilly Co, and Veloce BioPharma. B. McLellan has served as an investigator for Veloce BioPharma. S. Barone owns equity and is an employee of Veloce BioPharma. All other authors have declared no relevant conflicts of interest. O. Kukoyi declares that he has no conflict of interest. S. Goldfarb declares that she has no conflict of interest. M. Lacouture has a consultant/speaking role with Legacy Healthcare Services, Adgero Bio Pharmaceuticals, Amryt Pharmaceuticals, Celldex Therapeutics, Debiopharm, Galderma Research and Development, Johnson and Johnson, Novocure Inc., Lindi, Merck Sharp and Dohme Corporation, Helsinn Healthcare SA, Janssen Research & Development LLC, Menlo Therapeutics, Novartis Pharmaceuticals Corporation, F. Hoffmann-La Roche AG, AbbVie Inc., Boehringer Ingelheim Pharma Gmbh & Co. KG, Allergan Inc., Amgen Inc., E.R. Squibb & Sons LLC, EMD Serono Inc., AstraZeneca Pharmaceuticals LP, Genentech Inc., Leo Pharma Inc., Seattle Genetics, Bayer, Manner SAS, Lutris, Pierre Fabre, Paxman Coolers, Adjucare, Dignitana, Biotechspert, Teva Mexico, Parexel, OnQuality Pharmaceuticals Ltd., Oncoderm, Apricity, Novartis, and Our Brain Bank. Dr. Lacouture also receives research funding from Berg, Bristol-Myers Squibb, Lutris, Paxman, Novocure, US Biotest, and Veloce BioPharma.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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