Patients' Perceived Continuity of Care and Adherence to Oral Anticancer Therapy: a Prospective Cohort Mediation Study

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BACKGROUND: Oral anticancer therapy (OACT) poses adherence-related challenges to patients while generating a setting in which both primary care physicians (PCPs) and oncologists are involved in the active treatment of cancer. Continuity of care (COC) was shown to be associated with medication adherence. While maintaining COC is a central role of the PCP, how this affects continuity with oncologists, and jointly affects OACT adherence, is yet unknown.

OBJECTIVES: To explore how aspects of COC act together to promote OACT adherence. Specifically, to examine whether better personal continuity with the PCP leads to better personal continuity with the oncologist, which together lead to better cross-boundary continuity between the oncologist and the PCP, jointly leading to good adherence to OACT.

DESIGN AND SETTING: A prospective cohort study conducted in five oncology centers in Israel. A bootstrapping method was used to test the serial mediation model.

PARTICIPANTS: Adult patients (age > 18 years) receiving a first OACT prescription (n = 119) were followed for 120 days.

MAIN MEASURES: The Nijmegen Continuity Questionnaire was used to assess patients' perceived personal and cross-boundary continuity. The medication possession ratio was used to measure adherence.

KEY RESULTS: Better personal continuity with the PCP was associated with better personal continuity with the oncologist (B = 0.35, p < 0.001), which was associated with better cross-boundary continuity (B = 0.33, p < 0.001), which, in turn, was associated with good adherence to OACT (B = 0.46, p = 0.03). Additionally, the indirect effect of personal continuity with the PCP on adherence to OACT through the mediation of personal continuity with the oncologist and cross-boundary continuity was found to be statistically significant (B = 0.053, 95% CI 0.0006–0.17).

CONCLUSIONS: In a system where the PCP is the case manager, cancer patients' perceived personal continuity with the PCP has an essential role for initiating a sequence of care delivery events that positively affect OACT adherence.

KEY WORDS: continuity of care; adherence; oral anticancer therapy.

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INTRODUCTION

Oral anticancer therapy (OACT) refers to orally administered chemotherapy, hormonal, and targeted agents used for cancer treatment.[1] In recent years, OACT accounts for approximately 25% of all cancer pharmacological therapies.[2] The evolution of OACT as a common treatment model in cancer profoundly alters cancer care delivery,[3] by assigning significant parts of the treatment management to patients and caregivers,[4] and by inevitably generating a setting in which both primary care physicians (PCPs) and oncologists are involved in the active treatment phase.[5–7]

Alongside its advantages of increased patient autonomy and convenience, OACT poses challenges to patients' adherence.[8, 9] The intricacy of knowing the treatment dosing, side effects, and toxicities; of monitoring medication-taking; and of getting prescriptions refilled can be overwhelming to patients, and may hinder adherence to OACT and lead to disease progression and increased risk for death.[10] Adherence is defined as the extent of patients' conformity to the providers' recommendations about day-to-day treatment with respect to timing, dosage, and frequency.[11] Adherence to OACT has been evaluated in a broad range of OACT agents and cancer types,[12] and was found to be influenced by a multitude of factors.[13–15] Nonetheless, although continuity of care (COC) is an important component of effective and efficient cancer care, previously found to be associated with medication adherence among patients with chronic illnesses,[16–18] the literature lacks studies that examine how patients' experience with COC at the interface between primary and oncology care affects their OACT adherence.[19]

COC is defined as the degree to which a series of discrete healthcare events are experienced by the patient as coherent,

connected, and consistent with his or her medical needs and personal context. COC consists of various aspects, including personal (relational) continuity (the ongoing relationship between a patient and one or more providers), and cross-boundary continuity, also referred to as informational and management continuity (the communication and collaboration between care providers to connect care).[17, 18]

In the complex care setting of OACT, the PCP and the oncologist have different yet complementary roles. While the oncologist is responsible for the treatment plan, cancer patients expect the PCP to provide tailored information and advice about the treatment, and to address concerns and psychological needs.[6, 7] Moreover, an existing close relationship with a PCP is considered by patients to be an important foundation for cancer care provision.[20] Better cross-boundary continuity between the PCP and the oncologist, whether practiced by direct personal communication or via automated electronic technologies, may allow for timely and detailed transfer of patient and treatment-related information between physicians, patients, and families.[21, 22] When experienced by patients, better cross-boundary continuity may enhance their beliefs about OACT[23] and promote medication-taking behavior.[15]

Previous research addressed the various aspects of COC as distinct components.[24] However, for patients to experience good cross-boundary continuity, it has been suggested that first they must experience good personal continuity with the PCP and with the oncologist; that is, they must perceive each of the involved physicians as committed to them and as familiar with their personal conditions and preferences. This may be especially true in a gatekeeping setting, in which contacts with the healthcare system are directed by the PCP. In such systems, where the PCP is the patient's case manager, better PCP-role performance can promote patients' experienced personal continuity with the oncologist, by enhancing patients' trust in the oncologist, perceptions of knowing what to expect, and beliefs that nothing has been overlooked.[25]

Additionally, when the PCPs' whole-person knowledge of patients (perceived by patients as good personal continuity with the PCP) is translated into comprehensive documentation of patients' overall condition and care, especially within a system with universal usage of electronic health records and health information exchange system, the documented information can be used by other providers to better tailor the individual treatment plan.[26] This may be reflected in how patients perceive their personal continuity with providers and providers' collaboration.

This study's objectives were to explore how aspects of COC act together to promote OACT adherence. Specifically, we aimed to examine whether better *personal continuity with the PCP leads to better personal continuity with the oncologist, which together lead to better cross-boundary continuity between the oncologist and the PCP, which jointly lead to better adherence to OACT.*

METHODS

Study Setting, Design, and Population

This prospective cohort study was conducted in five oncology centers in Israel between July 2014 and October 2017.[27] Oncology care in Israel is provided mainly in outpatient centers, usually located in hospitals.[28] PCPs are employed by the health funds and act as the patient's case manager.[29] Clalit and Maccabi health funds, the two largest not-for-profit healthcare organizations in Israel, provide full medical coverage inclusive of pharmacy benefits for prescription medications.[30] Both operate integrated health information and communication systems built around shared electronic health records. Additionally, primary, specialist, and hospital services are connected via a health information exchange system (OFEK) that allows providers to automatically share and view patients' information between institutions and care settings.[31]

Following approval of the ethics committees of each participating center, of the University of Haifa, and of Clalit Health Services and Maccabi Health Services, written informed consent was obtained from all study participants. Patients, with all cancer types and in all stages of the disease, were invited by their oncology nurses in each oncology center to participate in the study. Patients were considered for the study upon receiving a first prescription for one of the following OACTs: chemotherapy (capecitabine, vinorelbine), targeted therapy (erlotinib, sunitinib, everolimus, ibrutinib, imatinib, ponatinib), hormonal therapy (abiraterone), or thalidomide-class agents (thalidomide and lenalidomide). These anticancer drugs were chosen to recruit a relatively large and representative sample of patients receiving OACT; they are used to treat the most prevalent cancer types, including breast, colorectal, lung, prostate, and renal cancers,[1] as well as some of the most common hematologic malignancies (e.g., chronic lymphocytic leukemia and multiple myeloma), and are covered under the national health services with no out-of-pocket costs to patients. Patients were excluded from the study if they were enrolled in a clinical trial, were diagnosed with cognitive deficits, or were unable to participate in a face-to-face or telephone interview because of hearing or language difficulties. Given an alpha error of 0.05, and a statistical power of 0.80, a sample size of 110 to 120 participants was calculated to detect differences in adherence rates (the outcome) using G*Power analysis for two independent means, based on estimates of 65 to 70% of good adherence rates.[9, 32]

Data Collection

Data collection occurred in three time points: upon recruitment (T0, baseline), 60 days after OACT initiation (T1, mid-follow-up), and 120 days after OACT initiation (T2, end-of follow-up). At T0, a survey was used to collect data on participants' sociodemographics, and information on disease-related and treatment-related factors were collected from patients' medical records in each center. At T1, the survey included information

about participants' health-related QOL and perceived COC. Four specifically trained individuals conducted the surveys in Hebrew, face-to-face or by telephone. Surveyors were blinded to information about participants' care providers and medication adherence to avoid interviewer bias. Data on prescription refills were retrieved from Clalit and Maccabi databases at T2.

Measures

Outcome. Adherence was calculated across all OACT types, using the medication possession ratio (MPR), a well-accepted measure of OACT adherence.[8, 9] MPR is defined as the total days' supply of medication, divided by the number of participation days (i.e., the number of treatment days between the index date and the end-of-study-period date). The index date was the date of first prescription dispensed. The end-of-study-period date was defined as 120 days after OACT initiation, or the date of OACT cessation, the earlier of the two. The value of the days' supply (in the nominator) was truncated if the supply extended beyond the study period. In the denominator, the number of treatment days was adjusted to the specific regimen of each medication, assuming a cyclic regimen of 14 days on medication followed by 7 days off medication for capecitabine and sunitinib; a 21-days-"on"/7-days-"off" regimen for lenalidomide and thalidomide; a once-a-week regimen for vinorelbine; and a continuous daily regimen for abiraterone, everolimus, ibrutinib, erlotinib, imatinib, and ponatinib.[8] MPR was dichotomized into poor adherence (MPR $\leq$ 0.8) and good adherence (MPR > 0.8). This cutoff point has been widely used in previous research[8] and is considered to reasonably stratify adherent and non-adherent patients.[33]

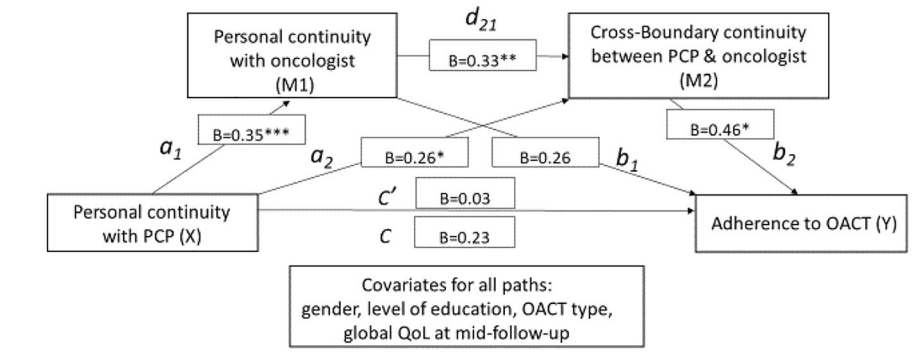
Predictor and Mediators. Participants' perceived COC was measured using the Nijmegen Continuity Questionnaire (NCQ), a valid and reliable generic questionnaire that measures patients' perceived COC as a multidimensional concept.[34] In the NCQ, responders are asked about their current experience with the PCP, and with the "most important specialist" (in this study, the oncologist), with whom they have been in contact over the past 12 months. The NCQ has three scales: (1) *personal continuity with the PCP* (8 items); (2) *personal continuity with the oncologist (the most important specialist)* (8 items); and (3) *cross-boundary continuity between providers* (the PCP and the current oncologist; 4 items). All NCQ items are scored on a 5-point Likert scale (1 = strongly disagree; 5 = strongly agree), with an option of "I do not know" scored as 0. Total scale scores are calculated as the mean of the items in each scale. The translation of the NCQ into Hebrew and its adaptation to the context of OACT is discussed elsewhere.[27] Items and subscale description of the NCQ are provided in Appendix 1 in the Supplementary Information. Data on all three scales were collected in T1, to allow participants without a prior history of oncology treatment to get acquainted with their oncologist and to reflect on their care experience while taking OACT.

Covariates. Potential covariates were factors previously reported in literature to be associated with OACT adherence,[8, 9] including patients' demographics: age, gender, level of education; health-related quality of life (QoL; measured by the EORTC QLQ-C30 global QoL score); and clinical characteristics: cancer type (grouped according to the affected body sites, i.e., breast, gastrointestinal system, kidney, lung, prostate, hematopoietic malignancies), cancer stage, previous oncology treatment, and OACT type (i.e., chemotherapy, targeted therapy, hormonal therapy, and thalidomide-class agents).

Statistical Analysis

Descriptive statistics were calculated for the entire sample and by level of adherence. We used listwise deletion to handle missing data; only participants with complete data on the predictor, mediators, and outcome were retained in analyses. Bivariate analyses were performed to estimate the association between each of the potential covariates and the predictor, the mediators, or the outcome using chi-square analysis (for the association between the outcome and categorical variables), *t* test, one-way analysis of variance (ANOVA; for the association between the outcome and continuous variables, and for the association between the predictor or mediators and categorical variables), and Pearson correlation (for the associations between the predictor or mediators and QoL). Pearson correlation was also used to measure the association between the predictor and each of the two mediators, as well as between the mediators.

To evaluate the suggested hypothesis, a serial multiple mediator model was constructed. The use of mediation analysis allows explaining the mechanism by which a predictor can lead to the outcome through the mediators based on hypothesized casual links between X, M1, M2, and Y. As shown in Figure 1, the model tests the pathway by which personal continuity with the PCP (the predictor, X) affects personal continuity with the oncologist (first mediator, M1), which affects cross-boundary continuity (second mediator, M2), which in turn affects adherence to OACT (outcome, Y). The total effect of personal continuity with the PCP (X) on adherence (Y) without the mediators in the model is represented by *c*; the direct effect of X on Y when all mediators (M1–M2) are included is represented by *c′*. The indirect effects of X on Y through the mediators (M1–M2) are represented by a1b1, a2b2, and a1d21b2 (the products of multiplying the coefficients of each path), and by the total indirect effect (C) (the sum of all indirect effects). Logistic regressions were used to estimate *c* (total effect), *c′* (direct effect), and paths b_1 and b_2 in the mediation model. Multiple linear regressions were used to estimate paths a_1, a_2, and d_{21} (Fig. 1). All regression analyses were controlled for all covariates that were found to be significantly associated ($p < 0.05$) with either the predictor, the mediators, or the outcome. The mediation model was tested using Preacher and Hayes's bootstrapping approach,[35] which allows more accurate estimates of confidence intervals because it is less susceptible to small sample size and



Direct effect of X on Y = c'

Effect	se	p	95% CI	
.0305	.2577	.9056	-.4745	.5355

Indirect effect(s) of X on Y:

	Effect	Boot SE	Boot 95% CI	
TOTAL (C)	.2665	.1541	.0283	.6454
Ind1 (a_1b_1)	.0936	.1079	-.0963	.3404
Ind2 (a_2b_2)	.1202	0980	-.0092	.3692
Ind3 ($a_1d_{21}b_2$)	.0527	.0445	.0006	.1711

Figure. 1 Serial mediation model of aspects of perceived continuity of care on adherence to OACT. Paths a_1 and a_2 estimate the association between the predictor (X) and each of the serial mediators (M1, M2), respectively. Paths b_1 and b_2 estimate the association between M1, M2, and the outcome (Y). Path d_{21} estimates the association between M1 and M2. Path *c* estimates the association between X and Y without the mediators in the model (the total effect). Path *c′* estimates the association between X and Y when the mediators are included in the model (the direct effect). Paths a_1b_1 and a_2b_2 represent the indirect effects of X on Y through M1 and M2 respectively. Path $a_1d_{21}b_2$ represents the indirect effect of X on Y through both serial mediators (M1–M2). B, unstandardized coefficient; OACT, oral anticancer therapy; PCP, primary care physician; QoL, quality of life. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. Indirect effects key: Total (C): the sum of all indirect effects (Ind1, Ind2, Ind3); Ind1: personal continuity with PCP -> personal continuity with oncologist -> adherence; Ind2: personal continuity with PCP -> cross-boundary continuity -> adherence; Ind3: personal continuity with PCP -> personal continuity with oncologist -> cross-boundary continuity -> adherence.

makes no assumption of the normality of the mediation paths.[36] Indirect effects were considered significant if the value zero was not included within the 95% confidence interval around the parameter of the indirect effect (based on 10,000 resamples).[37, 38] Analyses were performed using the SPSS version 23.0 statistical program (SPSS Inc., Chicago, IL). The mediation analyses were conducted using the PROCESS v3.2 macro for SPSS (Model 6).[39]

RESULTS

Of the 192 potentially eligible patients, 175 (91.1%) were members of Clalit and Maccabi health funds. Written consent was given by 150 (85.7%) patients. Of these, 56 (37.3%), 23 (15.3%), 23 (15.3%), 32 (21.3%), and 16 (10.7%) were recruited at the five oncology centers. Between T0 and T1, six patients (4.0%) died, in 17 patients (11.3%) OACT was discontinued, and eight patients (5.3%) were unable to complete the mid-follow-up (T1) questionnaire because of feeling too tired or not well enough. The final sample included 119 participants. Mean duration of OACT was 117.2 ± 19.3 days (range 56–120). MPR ranged from 0.22 to 2.0 (mean = 1.0 ± 0.28).

Table 1 presents participants' sociodemographics, clinical characteristics, and aspects of COC, in total and by level of OACT adherence. Overall, 25.2% ($n = 30$) had poor adherence to OACT (MPR ≤ 0.8) and 74.8% ($n = 89$) had good adherence (MPR > 0.8). As shown in Table 1, good adherence compared with poor adherence was found to be significantly associated with better *cross-boundary continuity* (2.1 ± 1.3 vs. 1.4 ± 1.3, respectively, $p = 0.01$) and with higher global QoL (56 ± 23 vs. 44 ± 24, respectively, $p = 0.02$).

Table 2 presents the bivariate analysis of the associations between the predictor, mediators, and potential covariates. As presented in Table 2, the three aspects of continuity were found to have significant correlations with each other ($r = 0.26$–0.36; $p < 0.001$ for all).[40] Additionally, gender, level of education, and type of OACT agent were significantly associated with aspects of COC (Table 2) and were included together with global QoL as covariates in the mediation model.

Figure 1 represents the serial mediation model of aspects of perceived COC on OACT adherence. The unstandardized regression coefficients of each path and covariates in the mediation model are reported in Table 3. According to the mediation model, better personal continuity with the PCP was associated with better personal continuity with the oncologist ($a_1 = 0.35$, $p < 0.001$), which was associated with better cross-boundary continuity ($d_{21} = 0.33$, $p < 0.001$), which was associated with good adherence to OACT ($b_2 = 0.46$, $p = 0.03$). Additionally, the indirect effect of personal continuity with PCP on adherence through personal continuity with the oncologist and cross-boundary continuity (indirect effect $a_1d_{21}b_2$) was found to be statistically significant ($B = 0.053$, 95% CI 0.0006–0.17), while all other indirect paths (a_1b_1, a_2b_2) were not statistically significant (Fig. 1; Table 3). As both the total effect (*c*) and the direct effect (*c′*) of personal continuity with the PCP on adherence to OACT were not significant ($B = 0.23$, $p = 0.32$; $B = 0.03$, $p = 0.91$, respectively), this may indicate that the effect of personal continuity with the PCP on adherence to OACT is fully mediated

Table 1 Patients' Characteristics and Aspects of Perceived Continuity of Care, in Total and by Level of Adherence to Oral Anticancer Therapy

Variables	Total, n = 119	Poor adherence (MPR ≤ 0.8), n = 30	Good adherence (MPR > 0.8), n = 89	p value
Predictor (X)				
Personal continuity with the PCP, mean (SD)	3.5 (1.0)	3.4 (0.8)	3.6 (1.0)	0.37
Serial mediators (M_1–M_2)				
Personal continuity with the oncologist, mean (SD)	3.4 (1.0)	3.1 (1.0)	3.5 (0.9)	0.08
Cross-boundary continuity between PCP and oncologist, mean (SD)	1.9 (1.3)	1.4 (1.3)	2.1 (1.3)	0.01
Potential covariates				
Age in years, mean (SD)	62.5 (12.4)	63.8 (13.7)	62.1 (12.0)	0.52
Gender, n (%)				
Female	72 (60.5)	15 (50)	57 (64)	0.17
Male	47 (39.5)	15 (50)	32 (36)	
Education, n (%)				
Academic or other higher education	80 (67)	19 (63)	61(68)	0.60
High school or less	39 (33)	11 (37)	28 (32)	
Health-related quality of life (EORTC QLQ-C30), mean (SD)				
Global quality of life score at mid-follow-up	53 (24)	44 (24)	56 (23)	0.02
Cancer type n (%)				
Breast	46 (39)	9 (30)	37 (42)	0.17
Gastrointestinal system*	44 (37)	13 (43)	31 (35)	
Prostate	11 (9)	2 (7)	9 (10)	
Lung	4 (3)	3 (10)	1 (1)	
Kidney	3 (2.5)	0 (0)	3 (3)	
Hematopoietic malignancies†	11 (9)	3 (10)	8 (9)	
Previous oncology treatment‡				
None	43 (36)	9 (30)	34 (38)	0.5
Any previous oncology therapy	76 (64)	21 (70)	55 (62)	
Cancer stage (for solid tumors only), n (%)				
Stage 4/metastatic disease	61 (57)	15 (56)	46 (57)	0.91
Stages 1 to 3	47 (43)	12 (44)	35 (43)	
Oral anticancer medication, n (%)				
Chemotherapy agents§	82 (69)	22 (73)	60 (67)	0.89
Targeted therapy agents	20 (17)	5 (17)	15 (17)	
Hormonal therapy agents¶	11 (9)	2 (7)	9 (10)	
Thalidomide-class agents#	6 (5)	1 (3)	5 (6)	

PCP, primary care physician; SD, standard deviation
**Gastrointestinal system malignances: colorectal, gastric, esophageal, and pancreatic carcinomas*
†Hematopoietic malignancies: multiple myeloma, chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia (CML)
‡Previous oncology treatment: radiation therapy (n = 5), chemotherapy (n = 28), or both (n = 43)
§Chemotherapy agents: capecitabine, vinorelbine
Targeted therapy agents: everolimus, sunitinib, erlotinib, ibrutinib, imatinib, ponatinib
¶Hormonal therapy agent: abiraterone
#Thalidomide-class agents: lenalidomide, thalidomide

Table 2 Bivariate Analysis of the Associations Between the Predictor, Mediators, and Potential Covariates

Variables	Personal continuity with PCP	Personal continuity with oncologist	Cross-boundary continuity between PCP and oncologist
	r	r	r
Personal continuity with PCP	1		
Personal continuity with oncologist	0.36*	1	
Cross-boundary continuity between PCP and oncologist	0.26*	0.34*	1
Global quality of life score at mid-follow-up	0.10	0.05	0.05
	mean (SD)	mean (SD)	mean (SD)
Gender (t test)			
Female	3.4 (1.1)†	3.3 (1.0)	2.0 (1.3)
Male	3.8 (0.80)	3.4 (0.9)	1.9 (1.5)
Education (t test)			
Academic or other higher education	3.5 (1.0)	3.4 (0.9)	2.1 (1.3)†
High school or less	3.6 (1.0)	3.4 (1.0)	1.6 (1.4)
Cancer type (ANOVA)			
Breast	3.3 (1.0)	3.4 (0.9)	2.0 (1.1)
Gastrointestinal cancer‡	3.7 (0.9)	3.2 (1.1)	1.7 (1.5)
Prostate	3.5 (0.8)	3.0 (0.7)	1.9 (1.4)
Lung	4.2 (0.5)	4.2 (0.7)	1.9 (1.7)
Kidney	4.0 (0.7)	3.7 (0.5)	1.3 (1.2)
Hematopoietic malignancies§	3.7 (1.2)	4.0 (0.7)	2.6 (1.5)
Previous oncology treatment			
None	3.7 (1.0)	3.4 (1.1)	1.5 (0.2)
Any previous oncology therapy	3.4 (1.0)	3.4 (0.9)	1.3 (0.1)
Cancer stage (for solid tumors only) (t test)			
Stage 4/metastatic disease	3.5 (1.0)	3.4 (1.0)	1.9 (1.3)
Stage 1 to 3	3.6 (0.8)	3.2 (0.9)	1.8 (1.4)
Oral anticancer medication type (t test)			
Thalidomide-class agents¶	3.7 (1.7)	4.1 (0.7)	3.7 (0.4)*
All other agents	3.5 (0.9)	3.3 (0.9)	1.8 (1.3)

**$p < 0.01$; †$p < 0.05$*
‡Gastrointestinal cancer: colorectal, gastric, esophageal, and pancreatic carcinomas
§Hematology malignancies: multiple myeloma, chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia (CML)
||Previous oncology treatment: radiation therapy (n = 5), chemotherapy (n = 28), or both (n = 43)
¶Thalidomide-class agents: lenalidomide, thalidomide
PCP, primary care physician; SD, standard deviation; r, Pearson correlation coefficient; ANOVA, analysis of variance

by personal continuity with the oncologist and cross-boundary continuity.[41, 42]

DISCUSSION

Study results support our hypothesis that personal continuity with the PCP has a pivotal, yet indirect effect on OACT adherence, through its effect on personal continuity with the oncologist, which in turn affects cross-boundary continuity.

Table 3 Results for the Regression Models in the Serial Mediation Analysis of Aspects of Perceived Continuity of Care on Adherence to OACT

		B	*SE*	*p*
		Outcome variable: personal continuity with the oncologist		
Total effect of personal continuity with the PCP on adherence to OACT				
Personal continuity with the PCP	Path a_1	0.35	0.09	<0.001
Personal continuity with the oncologist		—	—	—
Cross-boundary continuity		—	—	—
Covariates				
Gender (male)		0.03	0.17	0.85
Level of education (academic or other higher education)		0.01	0.18	0.96
OACT type (thalidomide-class agents)		0.72	0.39	0.07
Global QoL at mid-follow-up		− 0.0002	0.004	0.96
Constant		2.04	0.49	<0.001
		R^2 = 0.15, F(5.0, 113) = 4.04, p = 0.002		
Indirect effects	a_1b_1	0.09 (95% CI = −0.09 to 0.34)		
		Outcome variable: cross-boundary continuity		
Total effect of personal continuity with the PCP on adherence to OACT				
Personal continuity with the PCP	Path a_2	0.26	0.12	0.03
Personal continuity with the oncologist	Path d_{21}	0.33	0.12	0.008
Cross-boundary continuity		—	—	—
Covariates				
Gender (male)		0.15	0.22	0.50
Level of education (academic or other higher education)		0.72	0.24	0.003
OACT type (thalidomide-class agents)		1.84	0.51	<0.001
Global QoL at mid-follow-up		− 0.001	0.005	0.79
Constant		− 0.87	0.68	0.21
		R^2 = 0.27, F(6.0, 112) = 6.88, p < 0.001		
Indirect effects	a_2b_2	0.12 (95% CI = − 0.01 to 0.36)		
		Outcome variable: adherence to OACT		
Total effect of personal continuity with the PCP on adherence to OACT	Path c	0.23	0.24	0.32
Personal continuity with the PCP	Path c'	0.03	0.26	0.91
Personal continuity with the oncologist	Path b_1	0.26	0.25	0.29
Cross-boundary continuity	Path b_2	0.46	0.21	0.03
Covariates				
Gender (male)		0.61	0.47	0.19
Level of education (academic or other higher education)		− 0.20	0.50	0.68
OACT type (thalidomide-class agents)		− 0.87	1.26	0.49
Global QoL at mid-follow-up		0.02	0.01	0.02
Constant		− 2.66	1.50	0.07
		Nagelkerke R^2 = 0.18, p = 0.03		
Indirect effects	$a_1d_{21}b_2$	0.05 (95% CI = 0.0006 to 0.17)		

Paths a_1 and a_2 estimate the association between the predictor (X) and each of the serial mediators (M1, M2), respectively. Paths b_1 and b_2 estimate the association between M1, M2, and the outcome (Y). Path d_{21} estimates the association between M1 and M2. Path c estimates the association between X and Y without the mediators in the model (the total effect). Path c' estimates the association between X and Y when the mediators are included in the model (the direct effect). Paths a_1b_1 and a_2b_2 represent the indirect effects of X on Y through M1and M2 respectively. Path $a_1d_{21}b_2$ represents the indirect effect of X on Y through both serial mediators (M1–M2)
OACT, oral anticancer therapy; PCP, primary care physician; QoL, quality of life

Additionally, this study is the first to provide evidence for the importance of COC at the interface between primary and oncology care in the unique and evolving setting of OACT.

Although the total effect was not significant, the use of a serial mediation analysis allowed us to demonstrate the significance of the role of personal continuity with the PCP in initiating a sequence of healthcare-delivery events that affect patients' medication-taking behavior.[41] While other researchers also considered the various aspects of COC to have implicit value, it had been difficult to evaluate their unique contributions to health outcomes, especially when using indirect and proxy measures (such as continuity within site for cross-boundary/informational continuity, and proportions of encounters with the same clinician for personal/relational continuity).[18, 24] Moreover, COC is seen as part of patient-centeredness and addresses the extent to which healthcare is organized within providers and institutions and thus should be analyzed from the patient's perspective and not merely as a sequential account of same-provider visits.[43] In this study, we directly measured the various aspects of COC experienced by patients receiving OACT, allowing us to better differentiate between them from the patients' point of view and to study their sequential relations while affecting patients' medication-taking behavior.[34, 44] While this needs to be further investigated, our results may be applicable to other conditions, such as HIV[45] or rheumatoid arthritis,[46] that require extensive involvement of both the specialist provider and the PCP.

The current study has several limitations. The relatively small sample prevented the inclusion of more covariates in the model. Additionally, our study did not include individuals for whom OACT was discontinued or who were unable to take the follow-up survey, potentially resulting in an underestimation of poor adherence. This may affect study results and limit their generalizability. Nonetheless, prior studies that explored factors affecting adherence to OACT were also limited in sample size because of the advanced cancer stage and low

health status of the patients.[47, 48] As data collection occurred between 2014 and 2017, OACT was in its early stages in Israel, which had implications for patient availability. With the increasing use of OACT, future studies will be able to recruit larger samples, accounting for the length and amount of contact with providers, additional covariates, and nested designs of patients within medical centers. Additionally, the study was conducted in Israel, which may reflect similar primary care–based systems with universal use of electronic health records and health information exchange systems but might limit its applicability to other healthcare systems. Also, as this study examined perceived COC, it implies that, to affect outcomes, patients should acknowledge cross-boundary continuity, which often occurs outside their purview. Future research should examine whether patients' acknowledgment of COC versus other objective measures of care coordination has a differential effect on medication-taking behavior. Similarly, other forms of indirect and direct adherence measurements, such as self-report or serum concentrations, could complement MPR to maximize accuracy.[49]

The NCQ assesses patients' perceived COC with providers with whom they have been in contact over the past 12 months. Study results suggest that maintaining good personal continuity with the PCP prior to as well as throughout the active treatment phase of OACT may allow better adherence and improve treatment outcomes. This may be especially true when a long-lasting relationship with the PCP exists, leading to better COC. However, PCPs report losing contact with cancer patients and families when they enter the treatment phase because of uncertainty about their role, a lack of relevant training and knowledge, time and resource constraints, and inadequate information from the oncologists.[20, 50]

To overcome these barriers, healthcare-delivery organizations should support the involvement of PCPs in the care of their patients on OACT by acknowledging the need for increased contact time and frequency of consultations. Additionally, with the growing number of patients taking OACT, there is a need for educational modules for PCPs in OACT. Moreover, interprofessional interventions in which PCPs and oncologists could negotiate their roles and discuss communication strategies may promote cross-boundary continuity and improve OACT adherence and treatment outcomes.[51]

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