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RESEARCH

Time toxicity among older patients with cancer treated with palliative systemic therapy

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Abstract

Purpose The time toxicity of anticancer therapy, defined as days spent with healthcare contact during treatment, represents a critical but understudied outcome. This study aims to quantify time toxicity among older patients with cancer receiving palliative systemic treatment.

Methods All patients aged ≥ 65 years with metastatic cancer receiving cytotoxic chemotherapy, immunotherapy, or targeted therapy at a single center in Mexico were selected from a prospective patient navigation cohort. Patients completed a baseline assessment, including the G8 screening and quality of life measures. Physical healthcare contact days within the first 6 months were extracted from medical records and divided by days alive during the same period. Beta regression models were used to identify predictors of time toxicity.

Results We identified 158 older patients (median age 71 years); 86% received cytotoxic chemotherapy. Seventy-three percent had an impaired G8 score and were considered vulnerable/frail. Six-month overall survival was 74%. Within the first 6 months, patients spent a mean of 21% (95% confidence interval (CI) 19–23%) of days with healthcare contact. Concurrent radiotherapy (odds ratio (OR) 1.55; 95%CI 1.21–1.97), cytotoxic chemotherapy versus targeted therapy (OR 1.64; 95%CI 1.13–2.37), and an impaired G8 (OR 1.27; 95%CI 1.01–1.60) were associated with increased time toxicity.

Conclusion Older adults with metastatic cancer spend 1 in 5 days with healthcare contact during treatment, with a higher burden of time toxicity for patients receiving radiotherapy or cytotoxic chemotherapy and those with potential frailty. These findings underscore the importance of informing patients about their expected healthcare contact days within the context of a limited life expectancy.

Keywords Time toxicity · Healthcare contact days · Older adults · Metastatic cancer · Palliative systemic treatment

Introduction

Although outcomes for many tumor types have improved over the past decades, the additive survival benefits of most novel treatments for metastatic cancer have remained modest [1–3]. When making shared decisions with patients, these limited survival benefits need to be balanced with the potential downsides of therapy, such as side effects and impact on quality of life (QoL) [4]. An important yet understudied outcome that should also be taken into account is treatment-related time toxicity, which has been defined as the time spent on visits to healthcare facilities, seeking urgent care for side effects, hospitalizations, and follow-up tests [5, 6]. Time toxicity could significantly impact treatment choices in the context of limited survival time, and should be included in

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the decision-making process between oncologists, patients, and caregivers when starting anticancer treatments [7].

Due to multimorbidity, worse liver and renal function, and/or decreased bone marrow reserve, older patients with cancer have an increased risk of developing treatment-related toxicities compared to their younger counterparts [8, 9]. These toxicities and toxicity-related hospitalizations may contribute to a higher burden of time toxicity. Additionally, the survival benefits of palliative systemic therapy may be more marginal in older adults due to competing comorbidities, frailty, and socioeconomic factors [10, 11]. Since, in many cases, older adults value other outcomes over prolonging survival time [12–14], the burden of time toxicity may play a significant role in the decision making to start treatment. Yet, data on time toxicity in older patients with metastatic cancer are scarce. To address this evidence gap, studies investigating time toxicity are needed to determine how older patients receiving palliative systemic therapy spend their remaining time.

In Mexico, as in many low and middle-income countries (LMICs), many patients live far from the facilities where they are treated and must travel long distances to receive anticancer treatment [15]. A subset of patients must move with relatives near the hospital area for the duration of their treatment, while others rent a bed in shelters specifically set up for this purpose [16]. These circumstances may increase the time toxicity of anticancer treatment compared to previous studies conducted in developed countries. Therefore, this study aimed to quantify time toxicity in the initial 6 months of palliative systemic treatment among older Mexican patients with metastatic cancer, and to identify patient characteristics associated with a higher time toxicity.

Methods

Study design

Older patients undergoing palliative systemic therapy between August 2017 and November 2022 were selected from a prospective, ongoing patient navigation cohort (*Te Acompañamos*), designed to improve access to supportive and palliative care for patients with cancer. Study details have been extensively described previously [17, 18]. The cohort includes consecutive patients with recently diagnosed (< 3 months) metastatic solid cancer treated in the oncology clinic of *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (INCMNSZ), a public hospital in Mexico City, which has a broad catchment area encompassing the central region of the country. Participants were included within 2–3 weeks after treatment initiation and underwent basal supportive and palliative care needs assessments. Ethical approval for *Te Acompañamos* was obtained from the INCMNSZs Institutional Review Board. Since the patient navigation program is part of standard care for patients with advanced cancer at INCMNSZ, informed consent was waived.

For the current descriptive study, patients aged ≥ 65 years with metastatic cancer who started with palliative cytotoxic chemotherapy, immunotherapy, or targeted therapy within 90 days after inclusion were selected, excluding patients treated elsewhere or those receiving hormonal therapy, since time toxicity of such treatments differs from other antineoplastic therapies. Ethical approval of the INCMNSZ's Institutional Review Board was also obtained specifically for this retrospective analysis. The study was performed according to the STROBE guidelines and was conducted in accordance with the Declaration of Helsinki.

Study procedures

All participants underwent the following baseline assessments: the Functional Assessment of Cancer Therapy–General (FACT-G) for health-related QoL [19], Patient Health Questionnaire-2 (PHQ-2) to screen for depression [20], and Palliative Performance Scale (PPS) to estimate life expectancy [21]. The FACT-G measures four domains of health-related QoL in cancer patients, with high scores indicating a better QoL. Previous validation studies found a mean score of 82–87 in older adults with cancer, with an SD of 15–16 [22, 23]. Patients aged ≥ 65 years also completed the G8, designed to identify which older patients benefit from a geriatric assessment [24]. We considered all assessments performed within 90 days after inclusion.

Outcomes

The primary outcome was days with healthcare contact during the first 6 months after inclusion, collected from medical records. All days with physical visits to the INCMNSZ, including clinic visits, infusions, procedures, bloodwork, radiology/radiotherapy, emergency visits, and hospitalizations, were considered healthcare contact days, regardless of whether they were oncology-related or not. Video/telephone calls, multidisciplinary conferences, and missed/canceled appointments were excluded. Multiple visits on the same day counted as one contact day.

Secondary outcomes were overall survival (OS) and travel time from patients' homes to the hospital. Mean travel times were calculated using Google Maps, all measured at 08:00 AM on a Wednesday. In case of multiple transport routes, the shortest travel time was selected. For patients residing > 4 h away from the hospital, who may stay with relatives or in a shelter between healthcare contact days, the following criteria, derived from expert consensus, were established: if a patient spends ≥ 2 days in the hospital with

1 day in between, the day in between was counted as an additional day. If a patient spends ≥ 3 days in the hospital with 2 days in between, the 2 days in between were counted as two extra days.

Statistical analyses

Categorical variables were presented as frequencies and percentages, and continuous variables as medians with interquartile range (IQR) or means with a 95% confidence interval (CI) or standard deviation (SD). OS was calculated from inclusion date to the date of death using Kaplan–Meier. Time toxicity was calculated as healthcare contact days within the first 6 months divided by days alive within the same period. We stratified results based on frailty status, determined by the G8 score (cut-off for potential frailty ≤ 14 points).

To identify predictors of time toxicity, we used uni- and multivariable beta regression models with a logit link, which are appropriate for fractional outcomes restrained to values between 0 and 1. Odds ratios (OR) and their 95% CI were derived from β. Predefined clinically relevant predictors (treatment, number of agents, tumor type, and G8) and those with $p < 0.05$ in the univariable beta model were added to the multivariable model. Analyses were performed in SPSS v29 and R 4.2.2., with p-values of < 0.05 considered statistically significant.

Sensitivity analyses

During the COVID pandemic, telemedicine was widely adopted in Mexican clinical practice and access to resources and oncology care was reduced [25]. To address these pandemic-related changes, we conducted a preplanned sensitivity analysis in which patients enrolled between January 2020 and June 2021 were excluded. Another preplanned sensitivity analysis was performed in which travel time and extra days between hospital visits were not considered, aiming to increase the generalizability of the results to other settings.

Results

A total of 158 patients aged ≥ 65 years treated with palliative systemic therapy were included (Figure S1). Participants had a median age of 71 years (IQR 68–76), with 68 (43%) being male (Table 1). The majority ($N = 136$, 86%) received cytotoxic chemotherapy, 15 (10%) patients only received targeted therapy, and seven (4%) received immunotherapy. Eighty-six (54%) patients received two or more agents. Polypharmacy was reported in 99 (63%) patients and 41 (26%) screened positive for depression according to the PHQ-2. An impaired G8 score, indicating potential vulnerability/frailty, was found in 116 (73%) patients. The mean baseline FACT-G score for overall QoL was 70 (SD 14.5). Patients traveled a median of 73 min (IQR 35–112) to the hospital for a one-way trip, with 24% traveling more than 2 h to reach the hospital. Six-month OS was 74% and 12-month OS was 58%.

Time toxicity

Patients spent a mean of 21% (95% CI 19–23%) of their days during the first 6 months after diagnosis with physical health care contact, with the highest burden observed in the first month (Fig. 1). In the first 6 months after inclusion, 88 (56%) patients visited the emergency department at least once, with 49 patients (31%) visiting the emergency department at least twice. Forty-seven patients (30%) were hospitalized at least once.

Vulnerable/frail patients spent a mean of 22% (20–24%) of days with healthcare contact, with a time toxicity of 25% in the first month (Fig. 2). More than half (57%) visited the emergency department at least once and 33% were hospitalized at least once. Non-vulnerable/frail patients spent a mean of 18% (95% CI 16–21%) of days with healthcare contact, with 54% visiting the emergency department at least once and 26% being hospitalized at least once.

Predictors of high time toxicity

In univariable beta regression models, concurrent radiotherapy (β 0.31, OR 1.36; 95% CI 1.07–1.72, $P = 0.013$) and cytotoxic chemotherapy versus targeted therapy (β 0.48, OR 1.61; 95% CI 1.13–2.30, $P = 0.008$) were associated with a high burden of time toxicity, while overall QoL score was not (β − 0.01, OR 0.99; 95% CI 0.99–1.01, $P = 0.148$) (Table 2). In the multivariable model, concurrent radiotherapy (β 0.44, OR 1.55; 95% CI 1.21–1.97, $P < 0.001$), chemotherapy versus targeted therapy (β 0.49, OR 1.64; 95% CI 1.13–2.37, $P = 0.009$), and an impaired G8 score (≤ 14 points) (β 0.24, OR 1.27; 95% CI 1.01–1.60, $P = 0.039$) were associated with a high burden of time toxicity, while doublet or triplet therapy versus monotherapy was not (β 0.18, OR 1.20: 95% CI 0.96–1.48, $P = 0.106$).

Sensitivity analyses

To assess the impact of the COVID pandemic, all patients included between January 2020 and June 2021 were excluded, resulting in a mean time toxicity of 23% of days (95% CI 20–25%). A second sensitivity analysis was performed in which extra days between hospital visits were not counted as additional days with time toxicity for patients living far from the hospital. Mean days with healthcare contact

Table 1 Baseline characteristics ($N = 158$)

Variable	Category	
Age	Median years (IQR)	71 (68–76)
Sex, *n* (%)	Male	68 (43)
	Female	90 (57)
Primary tumor type, *n* (%)	Pancreas	28 (18)
	Colorectal	22 (14)
	Gastroesophageal	21 (13)
	Genitourinary	18 (11)
	Breast	12 (8)
	Gynecologic	11 (7)
	Cholangiocarcinoma	11 (7)
	Other	35 (22)
Type of palliative treatment, *n* (%)	Chemotherapy (with or without targeted therapy)	136 (86)
	Targeted therapy without chemotherapy*	15 (10)
	Immunotherapy (with or without cabozantinib)	7 (4)
Number of agents, *n* (%)	Single-agent therapy	72 (46)
	Doublet or triplet therapy	86 (54)
Concurrent radiotherapy, *n* (%)	Yes	28 (18)
Polypharmacy#, *n* (%)	Yes	99 (63)
	No	56 (35)
	Unknown	3 (2)
Weight loss during last 3 months, *n* (%)	No weight loss	48 (30)
	1–3 kg	28 (18)
	> 3 kg	74 (47)
	Unknown	8 (5)
Geriatric-8 score, *n* (%)	Normal (15–17)	39 (25)
	Impaired (≤ 14)	116 (73)
	Unknown	3 (2)
PHQ-2, *n* (%)	Normal (0–2)	101 (64)
	Impaired (3–6)	41 (26)
	Unknown	16 (10)
FACT-G score (mean, SD)	Overall score	70.0 (14.5)
	Physical well-being	18.7 (6.3)
	Social well-being	19.5 (4.2)
	Emotional well-being	16.2 (5.0)
	Functional well-being	15.7 (4.8)
	Unknown	23 (15)
Palliative Performance Scale	Life expectancy ≤ 6 months	48 (30)
Travel time (one-way trip)	Median minutes (IQR)	73 (35–112)
	0–2 h	120 (76)
	2–4 h	17 (11)
	4 h	20 (13)

*With or without the addition of hormonal therapy. #Four or more medicines derived from the G8 score. *FACT-G*, Functional Assessment of Cancer Therapy–General for quality of life; *SD*, standard deviation; *PHQ-2*, Patient Health Questionnaire-2 questionnaire for depression

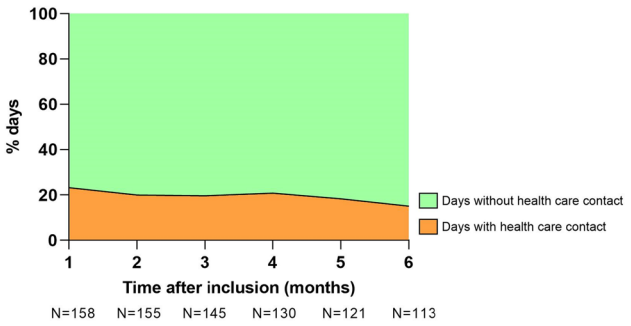

Fig. 1 Mean percentage of days with physical healthcare contact per month in the initial 6 months after inclusion in the cohort. Participants who died were censored per month

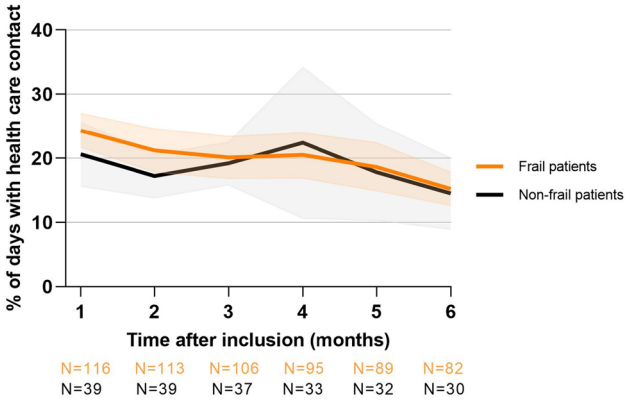

Fig. 2 Mean percentage of days with physical healthcare contact per month in the initial 6 months after inclusion in the cohort, stratified by frailty status (based on the G8 score). Participants who died were censored per month

days remained the same without considering these additional days (mean 21%, 95% CI 19–23%).

Discussion

Older adults with metastatic cancer spend 1 in 5 days with healthcare contact during the initial 6 months after diagnosis, with the highest time toxicity experienced in the first month. Patients receiving concurrent radiotherapy or cytotoxic chemotherapy, and those living with vulnerability/frailty had the highest percentage of healthcare contact days. These findings highlight the importance of discussing time toxicity in the decision-making process to start palliative anticancer treatment, particularly when treatments have marginal survival benefits which may be offset by time spent with healthcare contact.

To our knowledge, no previous studies have reported on the time toxicity of anticancer treatment in LMICs, and none have specifically explored it in older adults with metastatic cancer. Prior real-world studies were mostly performed in the USA and Canada. In a multicenter study of 362 patients with advanced pancreatic cancer treated with palliative chemotherapy in Pennsylvania, USA (median age 65 years), 10% of their days survived were spent with healthcare encounters in ambulatory care [26]. Bateni et al. found that, among 56 patients with metastatic melanoma receiving various treatment types in Ontario, Canada (mean age 68 years), time toxicity was 16% [27]. One study of 534 decedents with advanced gastrointestinal cancer receiving systemic therapy in Minnesota, USA, reported comparable results with a median of healthcare contact days of 25% [28]. Similarly, Gupta et al. studied time toxicity in 1985 Canadian decedents with stage IV non–small cell lung cancer receiving systemic therapy (median age 70 years) and found that 23% of their days were spent outside the home [29].

The high burden of time toxicity in our study compared to some previous ones may be attributed to differences in healthcare access between LMICs and developed countries. The fragmented healthcare system of Mexico, leading to inequities in access to care, often requires patients to travel long distances to obtain care [30]. This is underscored by our finding that patients spent a median of 73 min traveling to the hospital for a one-way trip, whereas a study in the USA found a median travel time of 32 min in older adults with cancer [31]. Limited access to cancer care and centralization of healthcare services in larger urban areas can thus contribute to a high time toxicity, as even a single hospital appointment can take an entire day [32].On the other hand, barriers to healthcare access could also lead to a lower time toxicity, which may be incorrectly interpreted as better care [33]. Future studies in LMICs incorporating information on healthcare access may help define the role of healthcare access in the measurement of time toxicity.

An impaired G8 score, indicating potential vulnerability/frailty, was associated with increased time toxicity. One reason for this higher time toxicity in patients with frailty may be their increased risk of treatment-related toxicities compared to those without frailty. Numerous studies have demonstrated that patients scoring low on the G8 have an increased risk of chemotherapy- and radiotherapy-related toxicities [34–36]. An impaired G8 score is also associated with postoperative complications [37, 38], emergency department visits [39], and more and longer hospitalizations [39, 40], all contributing to an increased time toxicity. To decrease hospitalizations and emergency visits, older adults with vulnerability/frailty may benefit from interventions aiming to lower treatment-related toxicities. Randomized controlled trials in older adults with geriatric syndromes have shown that upfront dose-reduced chemotherapy can lower chemotherapy-related toxicity and hospitalizations [41, 42]. Another option to lower time toxicity is the

Table 2 Associations between baseline characteristics and time toxicity

Variable	Category	Mean days	Univariable (β; OR (95% CI))	*p*-value	Multivariable (β; OR (95% CI))	*p*-value
Age	Continuous		0.00; 1.00 (0.99–1.02)	.695		
Tumor type	Gastro-intestinal	21.2	Ref		Ref	
	Other	20.6	−0.04; 0.96 (0.79–1.17)	.775	0.05; 1,05 (0.85–1.29)	.659
Treatment type	Chemotherapy	21.7	Ref		Ref	
	Immunotherapy	17.5	−0.15; 0.86 (0.54–1.38)	.533	−0.04; 0.96 (0.57–1.62)	.871
	Targeted therapy	14.7	**−0.48; 0.62 (0.44–0.89)**	**.008**	**−0.49; 0.61 (0.42–0.89)**	**.009**
Concurrent radiotherapy	No	19.8	Ref		Ref	
	Yes	25.7	**0.31; 1.36 (1.07–1.72)**	**.013**	**0.44; 1.55 (1.21–1.97)**	**< .001**
Number of agents	Single-agent	19.6	Ref		Ref	
	Doublet or triplet	22.0	0.16; 1.17 (0.97–1.43)	.100	0.18; 1.20 (0.96–1.48)	.106
Geriatric-8	Not impaired	18.4	Ref		Ref	
	Impaired	21.9	0.15; 1.16 (0.92–1.45)	.209	**0.24; 1.27 (1.01–1.60)**	**.039**
PHQ-2	Not impaired	20.3	Ref			
	Impaired	24.3	0.17; 1.19 (0.95–1.46)	.138		
	Unknown	15.8	−0.18; 0.84 (0.59–1.17)	.297		
FACT-G	Continuous		−0.01; 0.99 (0.99–1.01)	.148		
Polypharmacy	No	19.1	Ref			
	Yes	21.6	0.09; 1.09 (0.89–1.34)	.399		
Life expectancy (PPS)	> 6 months	19.9	Ref			
Travel time	≤ 6 months	22.8	0.09; 1.09 (0.89–1.35)	.412		
	Continuous		−0.00; 1.00 (1.00–1.00)	.730		

Results from the beta regression models with logit link, with the β representing the coefficients in log-odds and the with calculated odds ratio (OR) derived from the β and its 95% CI. *FACT-G*, Functional Assessment of Cancer Therapy–General for quality of life; *PHQ-2*, Patient Health Questionnaire-2 questionnaire for depression

implementation of a comprehensive geriatric assessment (CGA) and CGA-guided interventions. A CGA is a multidimensional process to identify medical, psychological, and functional needs to develop an integrated care plan and facilitate non-oncologic interventions [43]. Randomized trials have demonstrated that a CGA decreases severe toxicity, unplanned hospitalizations, and emergency presentations compared to usual care in older adults receiving systemic anticancer treatment [44–46]. Our findings underscore the importance of identifying vulnerable/frail patients before treatment initiation to improve patient-related outcomes.

The time toxicity of treatment is not routinely discussed when talking about the benefits and risks of palliative systemic therapy and patients' treatment goals. Given that patients who are adequately prepared for potential toxicities from anticancer treatment are more satisfied with their care [47], it is important to provide patients with a realistic understanding of how their life might be during therapy. Importantly, the finding of high time toxicity should not necessarily be interpreted as a criticism of cancer care. More time-toxic treatments are not incorrect by themselves, as each patient values the trade-off between quality and quantity differently. Certain time-consuming palliative treatments can indeed be effective and improve QoL. Furthermore, for some older and lonely patients, visiting the cancer center may be one of the only social interactions available to them. Hence, high time toxicity itself is not inherently negative. Nevertheless, it could be argued that all patients want to minimize time spent in waiting rooms and nights in the emergency department. Another argument for lowering time toxicity is that it may lead to an increased financial toxicity for patients and their caregivers due to increased travel and housing costs. Given that the financial burden of cancer is already substantial for most Mexican older patients with cancer due to limited government-funded insurance and availability of pensions [16], interventions aimed at reducing hospital visits could reduce financial toxicity.

A major strength of our study is that, to our knowledge, it is the first to evaluate time toxicity in older adults receiving palliative systemic therapy. We are the first to incorporate geriatric characteristics and study the association between the G8 and time toxicity. The observation that 73% of our study population had an impaired G8 score underscores that our cohort represents a frail group of older patients with cancer and results can be extrapolated to real-world practice. As no previous studies have been performed in LMICs, our findings represent a valuable step towards understanding this novel patient-centered outcome of time toxicity in these countries.

Our study also has some limitations. The extraction of healthcare contact days was limited to INCMNSZ, and we did not have access to data on visits to other hospitals or general practitioners. Additionally, we were unable to capture (waiting times for) pharmacy visits, potentially underestimating actual time toxicity. Due to its retrospective nature, our method of identifying patients with vulnerability/frailty was based solely on the G8, not specifically designed to measure frailty. Last, patients living at an address far from the hospital may have moved in with relatives, possibly leading to an overestimated time toxicity. However, one could argue that all time spent away from home is time-toxic. Moreover, the analysis not taking into account travel times resulted in a similar time toxicity. Despite gathering a heterogeneous cohort with various treatment types, our data represent the first evaluation of time toxicity in older adults with metastatic cancer, a patient population that constitutes a significant proportion of those currently being treated by oncologists. Future studies incorporating CGA to identify frailty more accurately, as well as qualitative studies exploring patients' expectations and experiences of time toxicity could further help in understanding this novel and important outcome.

Conclusion

Older adults with metastatic cancer spend 1 in 5 days with healthcare contact during the first 6 months after diagnosis, with a higher burden of time toxicity among patients receiving radiotherapy or chemotherapy and those living with vulnerability/frailty. Our findings underscore the importance of informing patients about their expected healthcare contact days within the context of a limited life expectancy. Time toxicity should be considered in the decision-making process to start palliative treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-024-08844-1.

Author contribution Conceptualization: ESP, Data curation; JB, PCR, ARM, AMA,WRL, VRC. Formal analysis: JB, Funding acquisition: JB. Investigation: JCB, YCG, WRL, ESP. Methodology: JCB, ESP. Project administration: PCR, YCG, AMA, WRL, ESP Resources: YCG, ESP. Supervision; YCG, ESP. Visualization: JCB. Roles/Writing—original draft: JCB, ESP. Writing—review & editing: all authors.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval Ethical approval for *Te Acompañamos* was obtained from the INCMNSZs Institutional Review Board. Ethical approval of the INCMNSZ's Institutional Review Board was also obtained specifically for this retrospective analysis.

Consent to participate Since the patient navigation program is part of standard care for patients with advanced cancer at INCMNSZ, informed consent was waived.

Competing interests The authors declare no competing interests.

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