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Time Toxicity of Patients with Cancer Enrolled in Clinical Trials – A Systematic Review and Meta-Analysis

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Abstract

Purpose: Time toxicity—the time patients spend receiving treatment, managing side effects, attending follow-ups, and undergoing rehabilitation—is increasingly recognised as an important burden of cancer care. While time toxicity has been studied in routine clinical settings, it has rarely been quantified among cancer patients enrolled in pharmacotherapy clinical trials. This systematic review aims to quantify time toxicity in this population.

Design: We searched Ovid MEDLINE, Embase, and Cochrane CENTRAL from inception to June 12, 2025. Studies were included if they reported on time toxicity among cancer patients enrolled in clinical trials. Time toxicity was defined as calendar days with healthcare contact. Primary outcomes were (i) total days, (ii) planned days, and (iii) unplanned days per month. Study quality was assessed using the JBI Checklist for Cohort Studies.

(Study protocol pre-registration: https://doi.org/10.17605/OSF.IO/BVY7C)

Results: Four retrospective studies reporting on an aggregate of 1,809 patients were included. Two studies had low risk for bias, and two had unclear risk of bias. Patients experienced time toxicity a mean of 7.6 days per month, with the highest burden in the first month of trial participation. Planned and unplanned days averaged 2.2 and 2.0 days per month, respectively. The ratio of planned to unplanned days remained consistent over time.

Conclusions: Time toxicity is a substantial, under-recognised burden in cancer pharmacotherapy trials—approximately twice that experienced by non-participants. Its measurement and mitigation should be prioritised to improve patient-centred care, support shared decision-making, and inform trial design, policy, and consent processes.

Key Messages

What is already known on this topic: Time toxicity is an increasingly recognised burden of cancer care but is rarely measured or reported in pharmacotherapy clinical trials, limiting informed decision-making.

What this study adds: This systematic review shows that trial participants experience substantial time toxicity—about 7.6 days per month, potentially double that of standard care—with both planned and unplanned healthcare contact contributing.

How this study might affect research, practice or policy: Routine measurement and reporting of time toxicity could improve informed consent, support shared decision-making, and encourage trial designs and policies that minimise patient burden.

Introduction

Globally, cancer accounts for approximately 20 million new cases and 10 million deaths per year, making it the most prevalent disease worldwide.[1] The majority of patients undergo treatment.[2]

Advances in therapy have improved survival, from a five-year survival of 49% in the 1970s to nearly 70% in the 2020s.[3] However, treatment is also associated with adverse effects, including dermatologic, endocrine, gastrointestinal, neurologic and hematologic complications.[4] It may also impair quality of life[5] and cause financial toxicity.[6,7]

"Time toxicity" has recently emerged as a concept to describe the time patients spend receiving treatment, managing side effects, attending follow-ups and undergoing rehabilitation.[8,9] This burden is particularly relevant for patients considering enrolment in pharmacological clinical trials, as their time commitments may differ from patients receiving standard care.

There has been limited reporting on time toxicity. A scoping review by Quinn et al found that time toxicity is rarely reported in oncology clinical trials and lacks a standardised definition, metric, or methodology.[10] However, the aforementioned review reports time toxicity predominantly amongst trials of oncologic surgery; no prior review has evaluated the additional time toxicity experienced by cancer patients enrolled in pharmacotherapy clinical trials. Such information may support informed decision-making by cancer patients and clinicians when considering trial participation, as they can evaluate whether they would like to invest the time towards trial participation.

The aim of this systematic review is to summarise the time toxicity experienced by patients with cancer enrolled in pharmacotherapy clinical trials.

Methods

A systematic review of studies reporting time toxicities among cancer patients enrolled in pharmacotherapy clinical trials was designed and the study protocol preregistered on an open repository (doi: https://doi.org/10.17605/OSF.IO/BVY7C) on June 11, 2025. This review is reported in accordance with the PRISMA 2020 statement.[11]

Eligibility Criteria

We included all studies reporting on time toxicity among patients with cancer enrolled in pharmacotherapy clinical trials. Time toxicity was defined as time spent coordinating and receiving antineoplastic treatment or trial-related procedures, managing side effects, attending follow-ups and undergoing rehabilitation.[8,9] Pharmacotherapy clinical trials were defined as trials enrolling patients with cancer to investigate drug treatments. Trials assessing treatments for adverse effects (e.g., alopecia, nausea and vomiting) and observational studies were excluded.

Outcome

The primary outcomes were (i) the days alive and spent in contact with the healthcare and research system, (ii) planned days spent in contact with the healthcare and research system, and (iii) unplanned days spent in contact with the healthcare and research system. The secondary outcomes were the methodology (including outcome measurement and statistical analyses) and outcomes of studies on time toxicity.

Search Strategy

We searched Ovid Medline, Ovid Embase and the Cochrane Central Register of Controlled Trials from inception to June 12, 2025, using key concepts related to cancer and time. The search strategy was reviewed by an information specialist and is detailed in Web Appendix 1. No language restrictions were applied. Backward reference searching of included articles was also conducted.

Screening

In level 1 (title and abstract) screening, articles were identified for further screening if they reported on cancer patients and time spent on care. In level 2 (full text) screening, studies were included if they were primary research involving cancer patients receiving pharmacotherapy and quantified time toxicity based on this review's predefined primary outcomes. Conference abstracts without corresponding full texts, reviews, case reports and letters

Following a calibration exercise using 20 articles to ensure concordance in applying eligibility criteria, two reviewers (RC, JHBI) independently screened studies through the two-stage process. Discrepancies were resolved through discussion and consensus, with a third reviewer (CZ) consulted as needed. All screening was conducted in Covidence.

Data Extraction

For each study, we extracted patient demographics (age, sex, country, cancer type), treatment characteristics (pharmacotherapy name; pharmacotherapy type of chemotherapy, immunotherapy,

targeted therapy or hormonal therapy), clinical trial phase, the methodology used to assess time toxicity, and reported outcomes.

The percentage of days per month, as reported by studies, was extracted for: (i) days alive and in contact with the healthcare system, (ii) planned days, and (iii) unplanned days. Data on planned and unplanned days were taken as reported, noting that one study did not account for all contact days across these two categories. Time toxicity was noted across the entire trial period, and monthly for the first six months of the trial. The days of time toxicity per month was calculated from the percentage, with one month defined as 30 days.

All data extraction was performed independently and in-duplicate by two reviewers (RC, JHBI) in Covidence. Discrepancies were resolved by discussion and consensus, with the input from a third reviewer (CZ) if needed. Corresponding authors were contacted (up to three times) if further data were potentially available. The extracted data are publicly available in an open repository.[12]

Quality Assessment

Study quality was assessed using the JBI Checklist for Cohort Studies.[13] In two studies where the underlying clinical trial was identified, the randomised trial was assessed using the Cochrane Risk of Bias version 2 (RoB 2) tool.[14] Quality assessment was conducted independently and in-duplicate by two reviewers (RC, JHBI), with discrepancies resolved through discussion and consensus; a third reviewer (CZ) was consulted if needed. Results were summarised graphically.

Data Synthesis

We conducted a thematic synthesis of the data. For the primary outcomes, a sample size-weighted average was calculated for each of three outcomes, across the total trial period. Subgroup analyses by country, pharmacotherapy type and clinical trial phase were not performed due to the small number of studies.

Results

Five papers[15-19] reporting on four studies of patients enrolled in clinical trials were included in this review (Figure 1). Two studies [Gupta 2023/24, Gupta 2023] reported on participants in phase 3 trials – Gupta et al. 2023/2024 reported on a predominantly-Canadian multicentre (30 Canadian centres, 2 USA centres, 1 Australia centre) clinical trial of patients with colorectal cancer receiving targeted therapy of cetuximab or supportive care (trial name: CCTG CO.17),[15,16] and Gupta et al. 2023 reported on a Canadian-based international multi-centre (26 Canadian centres, 10 USA centres, 18 Italian centers, 1 Australia centre) clinical trial of patients with non-Hodgkin's lymphoma receiving chemotherapy of gemcitabine or cytarabine (trial name: CCTG LY.12).[17] Two studies reported on patients with any cancer diagnosis enrolled in any phase 1-2 trial at their institution: one at an academic centre in Australia [Nindra 2023[18]] and one at an academic centre in the USA [Durbin 2024[19]].

Table 1 summarises the patient characteristics and methodology of the four retrospective cohorts. Sample sizes ranged from 219 to 610. Median ages ranged from 55 to 65. All studies reported time toxicity descriptively and defined it as any day involving contact with the healthcare system regardless of duration (i.e. one day could reflect a 1-hour appointment for bloodwork or a 3-hour appointment for chemotherapy). Three studies reported time toxicity stratified by planned

(protocol-specified) and unplanned days; one study [Gupta 2023[17]] did not. Three studies analyzed variation in time toxicity by patient and treatment characteristics, while one [Nindra 2023[18]] only reported descriptive results.

Quality assessment was conducted for the two identified clinical trials [Gupta 2023/2024[15,16], Gupta 2023[17]]. Both trials had low risk of bias. The four retrospective cohort studies were also assessed. Two [Gupta 2023/2024[15,16], Gupta 2023[17]] had an overall low risk of bias, with low risk in nine of eleven assessment domains. Two [Nindra 2023[18], Durbin 2024[19]] had unclear risk of bias, as four of eleven domains related to follow-up duration and completeness had insufficient reporting (Web Appendix 2).

All studies reported the average days per month in contact with the healthcare system during trial participation (Table 2), which ranged from 3.6 to 11.5 days (average 7.6 days). Three studies [Nindra 2023[18], Durbin 2024[19], Gupta 2023/2024[15,16]] reported monthly data, showing the highest time toxicity in the first month, followed by a decline in subsequent months (Figure 2). One study [Nindra 2023[18]] reported higher values than the other two; participants averaged 10.5 days (compared to under 7 days) in the first two months, and under 6 days (compared to under 4 days) thereafter.

Three studies reported on planned and unplanned days per month. Two [Gupta 2023/2024[15,16], Nindra 2023[18]] reported the breakdown during the entire trial (Table 2), with patients experiencing an average of 2.2 planned and 2.0 unplanned days. Gupta et al. 2023/2024[15,16] reported 0.81 unplanned days per each planned day, and Nindra et al.[18] reported a ratio of 0.97. Two studies

[Nindra 2023[18], Durbin 2024[19]] reported monthly data, showing the highest planned and unplanned days in the first month and decreasing over time (Figure 3). The ratio of planned to unplanned days remained consistent over time within studies but varies across studies; Nindra et al.[18] reported approximately half of total days as planned, and Durbin et al.[19] reported more than two-thirds of total days as planned.

Results from comparative analyses are summarised in Web Appendix 3. Two studies compared time toxicity between trial arms; Gupta et al. 2023/2024[15,16] found greater toxicity with the investigational agent compared to supportive care, while Gupta et al. 2023[17] reported no difference between the two investigational agents. Time toxicity varied by cancer type; Nindra et al.[18] reported the highest toxicity in thoracic cancer patients, and Durbin et al.[19] reported gastrointestinal cancer patients to experience the most toxicity. Greater time toxicity was associated with poorer patient outcomes, including greater decline in patient-reported physical function [Gupta 2023/2024[15,16]], reduced survival [Gupta 2023/2024[15,16], Durbin 2024[19]], and disease progression [Durbin 2024[19]]. Two studies compared pharmacotherapy classes but reached different conclusions; Nindra et al.[18] reported no difference between trials of targeted therapies and immunotherapies, whereas Durbin et al.[19] reported higher toxicity in targeted therapy trials.

Discussion

To our knowledge, this is the first systematic review to report time toxicity in patients with cancer enrolled in pharmacologic clinical trials. Patients spend on average 7.6 days per month participating in trial activities. Such time toxicity refers to the time patients spend receiving

treatment, managing side effects, attending follow-ups and undergoing rehabilitation, which can be both planned and unplanned.

We found that time toxicity is substantial among cancer patients enrolled in clinical trials and may exceed that experienced by patients not enrolled in trials. In routine care, cancer patients have been reported to experience between 2.3 to 5.3 days per month.[20,21] Our findings suggest that trial participants may experience a similar number of planned days, in addition to 0.8 to 1.0 unplanned days for each planned day. This may result in nearly double the total time toxicity compared to non-trial participants. Therefore, patients considering trial enrolment should be informed that their total time burden may be double that of cancer patients not enrolled in trials, for them to consider the added total time burden against possibly added survival benefit if the trial is more efficacious than standard care.

We reported that the ratio of planned to unplanned days varied across studies, possibly reflecting differences in how thoroughly trials were planned prior to enrolment. This ratio tended to remain stable over time, suggesting systemic omission of certain unplanned days throughout the trial period in the studies. For trialists, more comprehensive planning may enhance the ability to estimate total time toxicity based on planned contact time alone, providing for more accurate and transparent information during the informed consent process.

We also reported that time toxicity may vary across studies, potentially due to differences in patient and treatment characteristics. Patients with different cancers and types of pharmacotherapy may experience varying types of time toxicity. There is currently a limited body of literature for robust

subgroup analyses. In our small sample, one study of targeted therapy[15,16] reported lower time toxicity than the other trials on chemotherapy or any cancer pharmacotherapy. Among the two studies that included patients on any pharmacotherapy, the findings were inconsistent: one[18] reported no difference between targeted therapy and immunotherapy, while the other[19] reported greater toxicity with targeted therapy. These two studies also reported differing results by cancer type: one[18] reported thoracic cancer patients and the other[19] reported GI cancer patients experiencing the greatest time toxicity. Future studies can aim to further document time toxicity in cancer patients enrolled in clinical trials and analyze whether there are differences in time toxicity based on patient and treatment characteristics.

Greater time toxicity was associated with poorer outcomes of reduced physical function, shorter survival and increased disease progression. This suggests that time toxicity may not merely be a numerical value, but may also reflect the intensity of treatment or health deterioration. Therefore, an additional day of time toxicity may impose a greater burden on patients already experiencing high time toxicity, compared to those with lower baseline burden. These findings underscore the importance of not only measuring but also managing time toxicity, as it may serve as a surrogate marker for overall health outcomes.

Strengths and Limitations

This study has several strengths. We searched three databases without language restrictions, conducted screening, and data extraction in duplicate and independently by two reviewers, and adhered to a pre-registered protocol.[12] Reporting adhered to the PRISMA 2020 guidelines.[11]

The small number of included studies limited cross-study comparisons by cancer type, trial phase, or pharmacotherapy type. As a result, subgroup analyses of time toxicity were restricted to within individual studies. Further research is needed to assess time toxicity more comprehensively across diverse trial settings.

All included studies used retrospective cohort designs, which are susceptible to documentation bias and incomplete data capture. Future studies should incorporate prospective, pre-specified methodologies, recording time toxicity in real time during trial participation.

All studies involved clinical trials at either large academic centres or as part of multicentre trials. Trial settings were limited to Canada, the USA, Australia and Italy. This concentration in major centres limits the generalisability of findings, as patient experiences in community hospitals or regional centres may differ. Large academic centres typically have greater trial infrastructure, including dedicated research staff, coordinated scheduling, and on-site diagnostic and treatment services, which may reduce logistical burden. By contrast, patients at smaller centres may face greater time and financial toxicity due to fragmented care across multiple days, longer travel distances to referral centres, and fewer supportive resources. Future studies should therefore examine time toxicity in more diverse healthcare settings and geographic regions.

Moreover, defining one day of time toxicity as any day with healthcare contact treats all encounters equally, regardless of their duration or intensity. Consequently, a brief outpatient visit (e.g. a 15-minute blood draw) is weighted the same as a 24-hour hospital admission, potentially misrepresenting the true time burden on patients.[9] Future studies should aim for greater granularity

by measuring time toxicity in minutes or hours and distinguishing between encounter types (e.g. investigations, treatments, or trial-related procedures).

Implications for Patients, Clinicians, Researchers and Policymakers

Patients considering participation in cancer clinical trials should be informed not only about the conventional physical side effects but also time toxicity, namely that they may experience up to twice the time toxicity of non-participants. This may support more informed, values-based decision-making and help determine whether trial participation aligns with their personal preferences and life circumstances.

For clinicians, time toxicity should be incorporated into routine counselling for trial-eligible patients. Anticipating higher time demands, particularly in the first months, may help patients plan practically and emotionally for the intensity of trial participation. Clinicians can also advocate for supportive measures, such as streamlined scheduling and coordinated appointments, to help reduce patient burden.

For trialists, time toxicity should be recognised as a core patient-centred outcome. Rigorous planning may enable a more accurate estimation of the time toxicity expected, thereby providing more informed consent information. This level of reporting is typically required in published manuscripts as per the TIDieR checklist,[22] and should also be anticipated and included in study protocol and thereby the informed consent process. Prospective measurement would improve comparability across trials. Studies can also be adapted to minimise unnecessary time burden, such as through remote monitoring and reduced procedural intensity where possible.

For policymakers, incorporating time toxicity into trial evaluation frameworks could support a more holistic assessment of treatment value. Treatments that impose significant time toxicity without proportional clinical benefit may be less acceptable from both patient and system perspectives. Standardised reporting of time-related outcomes could improve trial transparency, support equitable access and inform health technology assessments.

In conclusion, this review highlights that time toxicity represents a meaningful burden experienced by patients with cancer enrolled in pharmacotherapy clinical trials, who may experience double the time toxicity of patients not on trials. The intensity of time demands, particularly early in trials, and their association with poorer outcomes, underscores the importance of recognising time toxicity as both a clinical and logistical consideration. Future trials should prioritise measurement, mitigation and transparent reporting of time toxicity to ensure that cancer care is not only effective, but also patient-centred and aligned with patients' values and preferences.

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Ronald Chow: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); validation (lead); visualization (lead); writing – original draft preparation (lead); writing – review & editing (lead)
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Carl Heneghan: Conceptualization (supporting); formal analysis (supporting); funding acquisition (supporting); project administration (supporting); supervision (equal); writing – review & editing (supporting)
Ronald Chow is the guarantor.

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Table 1. Summary of patient characteristics and methodologies of included studies

Study	n	Age	% Female	Cancer Diagnosis	Type of Pharmacotherapy	Clinical Trial Design	Time Toxicity Definition	Statistical Analysis
Gupta et al 2023[15], Gupta et al 2024[16]	572	Median: 63	36%	Colorectal Cancer	Targeted Therapy (Cetuximab)	Phase 3	- Time toxicity determined from resource utilization - 1 day defined as a day with any in-person contact with healthcare system (i.e., blood work, chemotherapy, physician visit, night in hospital, night in rehabilitation facility) - Time toxicity was subdivided into planned days pre-specified by protocol and unplanned days	- Descriptive statistics to summarize time toxicity per 28 days - Wilcoxon test to compare time toxicity between treatment arms - Multivariate linear regression to assess association between change in patient-reported outcome scores from baseline and time toxicity
Gupta et al 2023[17]	610	Median: 55	39%	Non-Hodgkin's Lymphoma	Chemotherapy (Gemcitabine, Cytarabine)	Phase 3	- Time toxicity determined from documented encounters with healthcare system - 1 day defined as a day with any in-person contact with healthcare system (i.e., blood work, chemotherapy, physician visit, night in hospital, night in rehabilitation facility)	- Descriptive statistics to summarize time toxicity in number of days and trial days - Wilcoxon test to compare time toxicity between treatment arms
Nindra et al 2023[18]	219	Median: 65	45%	Any Cancer	Any Pharmacotherapy	Phase 1 or 2	- Time toxicity determined from documented encounters with healthcare system - 1 day defined as a day with any in-person contact with healthcare system (i.e., blood work, chemotherapy, physician visit, night in hospital, night in rehabilitation facility) - Time toxicity was subdivided into planned days pre-specified by protocol and unplanned days (further subdivided into trial-related complications or cancer/treatment-related complications)	- Descriptive statistics to summarize time toxicity
Durbin et al 2024[19]	408	Mean: 60.6	57%	Any Cancer	Any Pharmacotherapy	Phase 1 or 2	- Time toxicity determined from documented encounters with healthcare system - 1 day defined as healthcare-associated days as either inpatient or outpatient - Time toxicity was subdivided into planned days pre-specified by protocol and unplanned days (further subdivided into inpatient and outpatient days)	- Descriptive statistics to summarize time toxicity - Paired t-tests and analysis of variance to assess univariable associations between patient characteristics and time toxicity - Multivariable regression models to identify independent predictors of time toxicity - Cox regression models to assess relationship between time toxicity and overall survival, progression-free survival, clinical benefit rate, overall response rate

Summary of patient demographics by study, with studies sorted by publication time. There are four studies, for which the first study has two publications.

Table 2. Median days per month in contact with the healthcare system during trial, as reported in studies

Study	Total Median Days Per Month (% of 30-Day Month)	Unplanned Median Days Per Month (% of 30-Day Month)	Planned Median Days Per Month (% of 30-Day Month)	Ratio of Unplanned to Planned Days
Gupta et al 2023[15], Gupta et al 2024[16]	3.6 (12%)	1.3 (4%)	1.6 (5%)	0.81/1.00
Gupta et al 2023[17]	11.5 (38%)	Not Reported		
Nindra et al 2023[18]	8.7 (29%)	3.8 (13%)	3.9 (13%)	0.97/1.00
Durbin et al 2024[19]	6.8 (23%)*	Not Reported		

**Mean value, as reported by study*

Four studies reported the percentage of days in contact with healthcare system during their trial period. Two studies further reported preplanned and unplanned days, as reported in this Table.