The timeliness of patients reporting the side effects of chemotherapy

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Journal: Supportive Care in Cancer

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Abstract

Purpose: To explore the actions cancer patients reported they would take in response to a range of common side effects of chemotherapy and whether these were considered appropriate based on current guidelines and evidence; and to explore the sociodemographic and cancer related variables associated with patients selecting the appropriate action (immediate medical attention or reporting) for two potentially life threatening side effects: fever, and unusual bleeding and bruising.

Methods: 436 medical oncology and haematology patients receiving chemotherapy completed two surveys to provide demographic, disease and treatment characteristics, and details on how they would respond if they experienced a range of specified side effects of chemotherapy (for example, nausea and vomiting, fatigue, and skin rash or nail changes). The proportion of patients reporting the appropriate action for each side effect was calculated. Multiple logistic regression examined the patient demographic and cancer characteristics associated with selecting the appropriate action (seeking immediate medical attention) for two potentially life-threatening side-effects of chemotherapy: high fever of 38 degrees Celsius or more, and unusual bleeding or bruising.

Results: Two-thirds of patients indicated that they would seek immediate medical attention for high fever (67%), but only 41% would seek immediate attention for bleeding or bruising. Cancer type and time since diagnosis were significantly associated with patients indicating that they would seek immediate medical attention for high fever; while time since diagnosis was the only variable significantly associated with patients reporting that they would seek immediate medical attention for unusual bleeding or bruising. For chronic side effects, like skin rash or nail changes, and tingling or numbness , which usually do not require urgent reporting, only between 12% and 16% would report them immediately. A significant proportion of patients reported that they would 'do nothing' about fatigue or tiredness (24%). By comparison, less than 10% patients reported that they would do nothing for the other side effects investigated.

Conclusions: Tools need to be created so that patients better understand the side effects after being treated with chemotherapy and what action they should take.

Key Words: chemotherapy, side effects, timeliness, self-reporting, quality of life

Relevance: Understanding how patients intend to report side effects allows the development of educational tools to help patients better understand the side effects of chemotherapy and the need to promptly report potentially life threatening side effects.

Introduction

Chemotherapy is an important component of cancer treatment and has contributed to improvements in cancer survival rates. Chemotherapy is associated with a range of side effects, with nausea and vomiting, fatigue, anaemia, hair loss, and changes in taste and smell being among some of the most common experienced [1].

It is important that patients report adverse effects from chemotherapy to their care provider. Some side effects may be able to be prevented or reduced, such as nausea and vomiting through the use of antiemetic prophylaxis [2]. Other side effects such as anaemia may require an adjustment in dosage or interval for subsequent cycles of treatment but are not urgent. [2]. Some serious side effects such as fever, infection, and unusual bruising or bleeding should be reported immediately to the health care team because of their association with prolonged hospitalisation, reduced quality of life, and death [3,4,5].

The reasons for some patients not reporting side effects may relate to a lack of awareness or education [6]. Many of the side effects of chemotherapy are experienced at home, particularly as hospital stays become shorter [7] and most recently patients are increasingly being treated as day patients. Therefore, patients and their families must be aware of what side effects to expect, and how to manage them, including when to seek medical advice [8]. Yet many patients and their families may regard side effects as inevitable and not be aware that adverse effects can be alleviated. Some patients believe that "good" patients don't complain, or they don't want to distract their doctor from administering treatment [9].

In Australia, chemotherapy education for medical oncology and haematology patients is typically provided by chemotherapy nurses, and involves both written and verbal information. Chemotherapy education usually takes prior to commencing chemotherapy if possible a day or two prior.

Recall of side effects also becomes an issue if the reporting is delayed [10]. For example, in a study by Coolbrandt et al, respondents reported fewer chemotherapy side effects and fewer severe side effects when self-report was delayed until the next hospital visit, compared to when symptoms were self-reported on each of the seven days immediately following chemotherapy administration [10]. There is also a discrepancy between patient and clinician reports of symptoms, with clinicians often underestimating both the number and severity of symptoms [11]. The use of structured side effect symptom lists rather than open-ended spontaneous reporting by the patient can help to improve reporting of side effects [12]. For example, one study found a ten-fold difference in the number of symptoms reported when a structured questionnaire was used, compared to spontaneous patient reporting. Another study reported the rates of detecting adverse drug reactions varied between 16% for spontaneous reporting, 24% for general enquiry, to 62% for specific questioning [9,13].

The aims of this study were:
a) To report the actions patients perceived they would take in response to a range of common side effects of chemotherapy;
b) To explore the sociodemographic and cancer related variables associated with patients selecting the appropriate action (immediate medical attention or reporting) for the two potentially life threatening side effects of fever, and unusual bleeding and bruising.

Methods:

Setting: The study was conducted in three medical oncology clinics (located in Victoria, Tasmania and Western Australia) and three haematology clinics (located in Queensland, New South Wales and

Victoria) in Australia. Clinics were in metropolitan areas and all were public hospitals. Ethics approvals were granted by the University of Newcastle Ethics Committee (H-2010-1324), the Cancer Institute NSW Population & Health Services Research Ethics Committee (ref: 2011/10/351), and the relevant hospital ethics committees.

Sample: Eligible patients were those attending a participating treatment clinic who: had a confirmed diagnosis of cancer; were aged 18 years or older; were English speaking; and were able to provide informed consent. Only participants who had received chemotherapy treatment for their cancer were included in the final sample. Those attending the clinic for the first time, or who were too unwell to complete the survey, were excluded.

Procedure: A research assistant provided a consecutive sample of eligible patients with written information about the study when patients presented for their outpatient oncology appointment. Informed consent was sought from all participants. Two surveys were conducted in an effort to minimise clinic disruption and reduce participant burden. Participants were asked to complete a brief paper and pencil survey in the clinic while they waited for their appointment. The survey included questions on sociodemographic, disease and treatment characteristics. Those who did not have time to complete the first survey in clinic were given the option of completing it at home and mailing the survey back to the researchers using a reply-paid envelope supplied. Participants were asked to complete a second mail out survey approximately one month later. The second survey contained questions on self-management actions for chemotherapy side effects. Non-responders were followed up by letter 3 and 6 weeks later.

Measures

Demographic variables: Age, gender, education, Indigenous status, marital status, country of birth, home post code, living situation, employment status, private health insurance status, concession card status, were obtained by patient self-report. Concession cards are government issued cards which allow access to lower cost health services and medicines.

Disease and treatment variables: Cancer type and time since diagnosis were assessed via patient self-report. Studies show a high level of agreement between self-reported cancer characteristics and medical records [14,15].

Knowledge of appropriate actions to take for chemotherapy side effects: Participants who had had chemotherapy were presented with the following introduction: “Chemotherapy often has side-effects. The following questions ask about how you would manage chemotherapy side-effects at home. You may not have experienced all of these side-effects. If this is the case, please still tell us what you think you would do if this happened to you.” Respondents were asked “What action would you take if, following chemotherapy you experienced….”and were presented with a list of common side effects of chemotherapy. Response options included: call or go to the hospital immediately; call or go to the hospital if it hasn’t improved after a few hours; call or go to the hospital if it hasn’t improved after a few days; make an earlier appointment with my cancer doctor; wait until my next appointment with my cancer doctor, do nothing. Participants attending medical oncology centres also had an additional response category “make an appointment with my GP in the next day or two.”

Appropriate responses based on the American Cancer Society advice which informs patients and relatives about the related toxicities from evidence-based guidelines were assigned to each side effect by the expert medical oncologist on the team (IO) [16]. The potentially rapidly life-threatening side effects which should be reported immediately are a high fever, and bleeding or bruising. Symptoms that should be reported promptly (usually within a few hours), if severe, included flu-like

symptoms, sore mouth, or soreness in the vein, because they can become serious if they progress. Other side effects like diarrhoea, nausea and vomiting, constipation and pain can be alleviated with treatment. In order to improve quality of life during treatment, such symptoms should be reported if they persist over hours or days, depending on their severity. Other side effects such as a rash or nail changes, tingling or numbness, and fatigue, are more chronic and due to a gradual onset of cumulative toxicity after therapy Worry about the severity of these may occasion making an earlier appointment but they do not, in general, require urgent reporting [16].

Statistical analysis

Sociodemographic, disease and treatment characteristics, and patient survey responses were summarized as frequencies and percentages.

Two multivariable logistic regression analyses were undertaken to assess patient demographic and disease characteristics associated with patients indicating that they would call or go to hospital immediately for the serious side effects high fever; and unusual bleeding or bruising. For the logistic regressions, a binary outcome variable was defined. Selecting "call or go to hospital immediately" was coded as correct and all other responses were coded as incorrect.

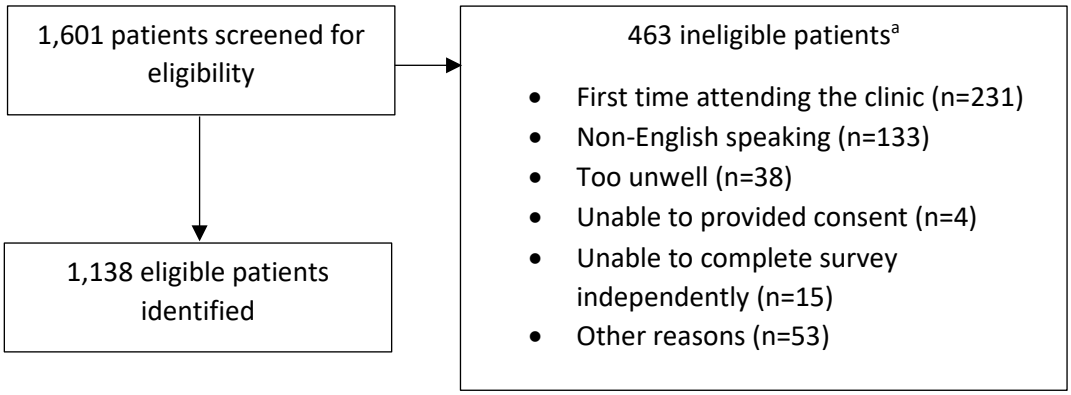
A hypothesis-driven approach was used for the selection of patient demographic and cancer characteristics included in the multivariable logistic regressions: sex, age, education, concession card, cancer type (which was coded as: breast, colorectal, non-Hodgkin's lymphoma and other) and time since diagnosis and treatment centre was accounted for in the models through the clustered-jackknife method [17,18,19]. Adjusted odds ratios (ORs) with 95% CIs and type 3 p-values are presented. Associations with $p<0.05$ were considered statistically significant. Listwise deletion was used to remove observations with missing data so that only participants with complete data on all relevant variables were included in the multivariable analyses.

Results

Figure one provides an overview of the recruitment process of eligible consenting participants into this study. Of the 1138 eligible patients identified, 898 (79%) provided consent, of which 436 completed both surveys and indicated that they had had chemotherapy treatment and were thus included in the analysis.

There were no significant differences between consenters and non-consenters with regards to sex $p= 0.23$) or age ($p= 0.53$).

Just over half of participants in this study were female, aged between 55 and 74 years and had a vocational training, university or other level education. The most commonly reported cancer type was other, followed by breast cancer. A detailed description of the sociodemographic, disease characteristics of participants is presented in Table 1.



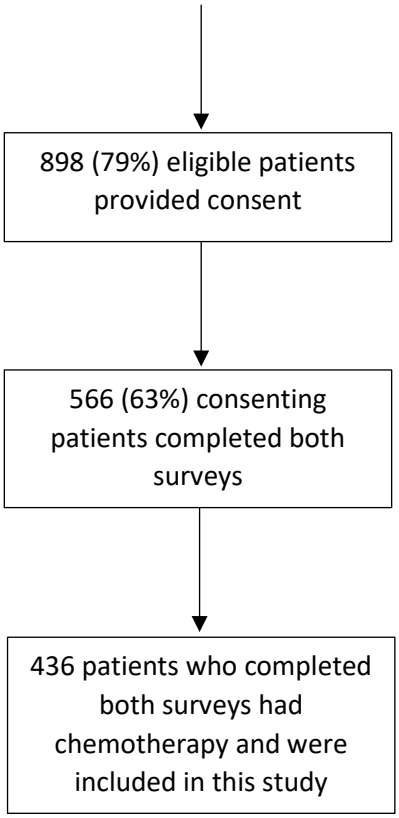


Figure 1. Overview of patient recruitment

[a]Patients could be classified as ineligible for multiple reasons, thus individual categories may not add up to total number of ineligible patients.

Table 1. Sociodemographic and disease characteristics of participants

Variable	Subgroup	Total (N=436)
Sex	Male	187 (43%)
	Female	249 (57%)
Age	< 55	133 (31%)
	55 to 74	245 (57%)
	>=75	54 (13%)
Indigenous status	Non indigenous	423 (98%)
	Indigenous	7 (1.6%)
Marital status	Married or partner	276 (64%)
	Single, divorced, separated or widowed	155 (36%)
Highest level of Education	High school or below	206 (48%)
	Vocational training, university or other	225 (52%)
Country of Birth	Australia	306 (71%)
	Others	127 (29%)
Insurance	Yes	166 (38%)
	No	266 (62%)
Concession card	Yes	253 (59%)
	No	177 (41%)
Rurality	City	364 (84%)
	Regional or Remote	68 (16%)
Living arrangements	Lives with spouse	297 (69%)
	Lives alone	92 (21%)
	Lives with other family members	29 (6.7%)
	Unrelated	12 (2.8%)
	Other	2 (0.5%)
Employment	Home duties, unemployed, retired, disabled	265 (61%)
	Full or part time work	144 (33%)
	Other	25 (5.8%)
Cancer Type	Breast	120 (28%)

Variable	Subgroup	Total (N=436)
	Colorectal	52 (12%)
	Lung	27 (6%)
	Prostate	14 (3%)
	Melanoma	7 (2%)
	Non-Hodgkin lymphoma	46 (11%)
	Myeloma	27 (6%)
	AML	18 (4%)
	CLL	15 (3%)
	MDS	7 (2%)
	CML	6 (1%)
	ALL	2 (0%)
	Haematology other	13 (3%)
	More than one other type	64 (15%)
	Missing	6 (1%)
Time since diagnosis	12 months or less	163 (38%)
	13-24 months	76 (18%)
	24+ months	195 (45%)

Table 2: Number and percentage of respondents endorsing each response to experiencing a chemotherapy side effect (n= 436)

What action would you take if, following chemotherapy, you experienced...	Call or go to hospital immediately	Call or go to hospital if it hasn't improved in a few hours	Call or go to hospital if it hasn't improved after a few days	Make an appointment with my GP in the next day or two OR make an earlier appointment with my cancer doctor	Wait until my next appointment with my cancer doctor	Do nothing
Nausea or vomiting	35 (8.5%)	141 (34%)	86 (21%)	69 (17%)	58 (14%)	21 (5.1%)
Diarrhoea	15 (3.7%)	101 (25%)	131 (32%)	74 (18%)	60 (15%)	26 (6.4%)
Fatigue or felt tired	5 (1.2%)	15 (3.6%)	45 (11%)	72 (18%)	176 (43%)	98 (24%)
Constipation	8 (2.0%)	21 (5.2%)	123 (30%)	113 (28%)	102 (25%)	40 (9.8%)
A sore mouth or throat	12 (3.0%)	31 (7.7%)	113 (28%)	108 (27%)	114 (28%)	26 (6.4%)
A high fever (38 degrees Celsius or more)	276 (67%)	91 (22%)	19 (4.6%)	22 (5.3%)	3 (0.7%)	3 (0.7%)
A rash or other skin and nail changes	49 (12%)	45 (11%)	94 (23%)	81 (20%)	118 (29%)	19 (4.7%)
Pain or burning	96 (24%)	128 (32%)	78 (19%)	54 (13%)	40 (9.9%)	9 (2.2%)
Tingling or numbness	64 (16%)	83 (20%)	72 (18%)	62 (15%)	110 (27%)	16 (3.9%)
Unusual bleeding or bruising	167 (41%)	112 (27%)	53 (13%)	52 (13%)	17 (4.2%)	7 (1.7%)
Flu like symptoms such as fever or cough	119 (29%)	92 (22%)	84 (21%)	65 (16%)	41 (10%)	8 (2.0%)
Soreness in my vein (where the chemotherapy was given)	94 (24%)	105 (26%)	84 (21%)	39 (9.8%	58 (15%)	19 (4.8%)

Proportion of patients reporting they would take the recommended action in response to chemotherapy side effects

Table 2 describes the actions that patients reported they would take in response to the range of potential chemotherapy side effects. The two side effects that can rapidly become life-threatening and should be reported immediately are high fever, and unusual bleeding and bruising. Most patients (67%) indicated that they would call or go to the hospital immediately for high fever, but only 41% would report unusual bleeding or bruising immediately.

Other side effects that should be reported within a few hours if they are severe are 'flu-like symptoms a sore mouth or throat, and persisting soreness in the vein. A sore mouth or throat can indicate mouth ulcers, which are a potential portal for infection and therefore need symptomatic treatment. Persisting soreness in the vein can indicate extravasation (leakage of fluid into the tissues). Most of the respondents indicated they would report these side effects within a few days, except for a sore mouth or throat, where only 38.7% indicated they would report it within a few days or sooner.

For potentially treatable side effects where treatment can improve quality of life, pain was most likely to be reported quickly, with 56% reporting immediately or within hours. Sixty percent of participants would report diarrhoea within days or sooner, but only 37.2% with constipation would contact the hospital within days, and 28% would seek advice from their GP within days.

For more chronic side effects like skin rash or nail changes, which usually do not require urgent reporting, only 12% would report them immediately- which is appropriate. By comparison less than 10% patients reported they would do nothing for other side effects, except for fatigue or tiredness where 24% would not take steps to report it.

Characteristics associated with correct action on the most serious side effects of high fever or unusual bleeding or bruising

Results are presented from the multivariable logistic regression analyses assessing the association between patient characteristics and patient's indicating that they would call or go to hospital immediately for the potentially rapidly life-threatening side effects of high fever (table 3) and unusual bleeding or bruising (table 4)

A total of 399 patients had complete data for the side-effect high-fever and were thus included in this analysis. As shown in Table 3, cancer type and time since cancer diagnosis were the only two characteristics found to be statistically significantly associated with patients indicating that they would call or go to hospital immediately in the case of experiencing a high fever. Patients with non-Hodgkin lymphoma had more than four times the odds (OR: 4.01; 95% CI 1.2 to 13.6) of selecting the recommended action than patients diagnosed with 'other' cancers (p=0.004). Patients diagnosed with cancer more than 24 months ago had significantly lower odds of selecting the recommended action (OR: 0.51; 95% CI 0.3 to 0.9) compared to patients who were diagnosed 12 or less months ago.

A total of 394 patients had complete data for the side effect unusual bleeding or bruising and were thus included in this analysis. As shown in Table 4, time since diagnosis was the only characteristic found to be statistically significantly associated with patients indicating that they would call or go to hospital immediately for this side effect. Specifically, patients who were diagnosed 24 months or more ago had statistically significantly lower odds of selecting the recommended action (0.53; 95% CI 0.3 to 0.8) than patients who were diagnosed 12 or less months ago.

Table 3. Sociodemographic, disease and treatment characteristics associated with participants selecting that they would 'call or go to the hospital immediately' in response to high fever

Variable	Subgroup	OR (95% CI)	p
Sex	Female	1.65 (0.8 to 3.3)	0.0691
	Male	.	
Age	55 to 74	1.15 (0.3 to 3.8)	0.1499
	>=75	0.67 (0.1 to 6.6)	
	< 55	.	
Education	Vocational training, University or other	0.76 (0.3 to 1.8)	0.4219
	High school or below	.	
Cancer Type	Breast	0.96 (0.5 to 1.8)	0.0036
	Colorectal	1.40 (0.5 to 4.1)	
	Non-Hodgkin lymphoma	4.01 (1.2 to 13.6)	
	Other	.	
Time since cancer diagnosis	13-24 months	0.47 (0.1 to 2.4)	<.0001
	24+ months	0.51 (0.3 to 0.9)	
	12m or less	.	
Concession card	Yes	1.26 (0.6 to 2.6)	0.4077
	No	.	

Table 4. Sociodemographic, disease and treatment characteristics associated with selecting that you could 'call or go to the hospital immediately' in response to unusual bleeding or bruising

Variable	Subgroup	OR (95% CI)	p
Sex	Female	1.33 (0.6 to 2.9)	0.3594
	Male	.	
Age	55 to 74	0.76 (0.4 to 1.4)	0.0566
	>=75	0.68 (0.4 to 1.0)	
	< 55	.	
Education	Vocational training, University or other	0.76 (0.4 to 1.4)	0.2721
	High School or below	.	
Cancer Type	Breast	1.26 (0.8 to 2.1)	0.6363
	Colorectal	0.89 (0.3 to 2.8)	

Variable	Subgroup	OR (95% CI)	p
	Non-Hodgkin lymphoma	1.30 (0.3 to 5.3)	
	Other	.	
Time since diagnosis	13-24 months	0.68 (0.2 to 2.3)	0.0001
	24+ months	0.53 (0.3 to 0.8)	
	12m or less	.	
Concession card	Yes	1.30 (0.8 to 2.1)	0.1783
	No	.	

Discussion

It is critical that patients undergoing chemotherapy have a thorough understanding of the potential toxicities of their treatment, and that they know what action to take if they experience a side-effect. Taking the appropriate action will improve quality of life while receiving chemotherapy, and may also improve survival [3,4,5]. This study shows that there is scope for increasing the proportion of patients reporting potentially serious side effects in a timely manner.

Fever and unusual bleeding or bruising are two of the most potentially serious side effects of chemotherapy. These life-threatening side effects should receive immediate medical attention. Neutropenic fever can lead to longer hospitalisation times if antibiotic treatment is delayed, and between 2% and 21% of patients will die if left untreated [20,21]. Unusual bleeding or bruising, often due to low platelet counts after chemotherapy, can increase patient risk of life-threatening spontaneous haemorrhage, and also limit future chemotherapy doses and frequency [22]. While in this study it is encouraging that both fever and unusual bleeding or bruising had the two highest proportions of patients reporting that they would contact the hospital immediately, the number of participants who indicated that they would not take immediate action for these side effects is concerning. Almost one third of participants indicated that they would not take immediate action for fever, and less than half of participants indicated that they would seek immediate help for unusual bleeding or bruising.

These findings suggest that a sizeable proportion of chemotherapy patients may not be well informed or do not recall or do not understand the information given about serious side effects and potential adverse events related to their treatment. Alternatively, it is possible that the findings indicate that patients are aware of what to report but do not intend to do so. The suggestion of not being informed or not recalling or understanding the information given is more likely and aligns with research by Hershman and colleagues who performed a study to explore patients' perceptions of physician-patient discussions of adverse events [23]. Common side effects, including tiredness, nausea and vomiting, and loss of appetite, were discussed with patients prior to chemotherapy more than 80% of the time. However less common but more serious adverse events, such as fever with low white cell counts, were discussed less frequently. Also, whereas 76% of patients reported having discussed neutropenia, only 68% reported understanding the information "completely" or "very well". The events most commonly discussed in Hershman's study were the ones most often experienced. Other studies have found correlations between the expectation of subjective toxicities and the subsequent reporting of that toxicity [24]. The issue of not retaining or understanding education sessions is underpinned by a literature review in the nursing literature which shows that there are many ways to provide information but retention is based on individual patients' preference [25]. In the Australian setting, although there is a paucity of studies

reporting the evaluation of nursing education about anticancer chemotherapy a small survey showed that 70% of the responders agreed or strongly agreed that the education had been beneficial [26].

Longer time since diagnosis was associated with lower odds of selecting the recommended action to take in response to unusual bleeding or bruising. This may reflect a familiarity with toxicities by patients over time and greater confidence in dealing with these. It is also possible that patient education for managing potentially serious side effects is emphasised more for newly diagnosed patients, but that such information may not be retained by patients over time. Health professionals may erroneously assume that patients who have had a previous course of chemotherapy already have this knowledge.

Compared to participants with other diagnoses, those with non-Hodgkin lymphoma were more likely to indicate that they would seek help immediately in response to a high fever. This finding may be the result of differences between education provided to those with potentially curable cancer who are often treated more intensively, and others. It may also reflect differences in the types of information provided by haematologists and oncologists.

No sociodemographic characteristics were associated with actions in response to the hypothetical chemotherapy side effects. This contrasts with findings from previous studies. For example, Hershman et al found that black patients had less physician discussion than white patients, and previous research shows a lower survival rate in black patients, but little is known about the link between adverse events and survival [23,27]. In a study recording adverse events to cancer therapy using patient journals, women spontaneously reported many more side effects than men [28], although in the current study women were not more likely to report serious side effects than men. This may reflect differences in the study methods, for example, prospective reporting versus hypothetical reporting.

A potential limitation of the current study is that it only included patients treated in urban hospitals. Further research with more diverse samples of participants including more of lower socioeconomic status may be warranted. We acknowledge the need to balance the desire to pursue rigorous detail in a patient reported survey with the practical need to have the survey simple enough to be able to be completed by a large sample of patients attending a cancer treatment clinic. In the current study, patients were not asked to consider varying levels of symptom severity, given that this would have added length and complexity to the survey. This is a further study limitation, as the actions of patients are likely to be influenced by their perceptions of symptom severity. Similarly, no distinction was made between symptoms of nausea and vomiting, which may otherwise present different experiences for the patient and need for urgency of action. Finally, the survey was developed specifically for this study, and while based on a review of the literature and consultation with experts in the field, it is not a validated tool for the assessment of patient responses to potential side effects of chemotherapy treatment. Such a tool should be developed for future research in this area.

Given the importance of timely and accurate reporting of side effects experienced following chemotherapy, it is critical that strategies are implemented to ensure patients know how to appropriately respond to serious side effects they may experience. Several interventions incorporating electronic methods of patient self-report of side-effects have been tested. These mobile healthcare solutions allow patients to report, in real time, the prevalence and severity of the side effects they are experiencing with feedback of this information to healthcare providers that are then able to initiate appropriate management of the reported symptoms [29]. The findings of this study support the need for ongoing efforts to improve patient responses for appropriately managing the side effects of chemotherapy. An in-depth qualitative study would offer a useful next step in determining why patients may or may not choose to act on specific symptoms.

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Acknowledgements

This research was supported by a National Health & Medical Research Council (NHMRC) Project Grant (ID 1010536), a Strategic Research Partnership Grant (CSR 11-02) from Cancer Council NSW to the Newcastle Cancer Control Collaborative (New-3C), and infrastructure funding from the Hunter Medical Research Institute (HMRI). Our thanks to the participating cancer treatment centres; Rochelle Smits, Alison Zucca, Heidi Turon and Hannah Small for research support; Sandra Dowley for data management; and Tiffany Evans or statistical assistance. A/Prof Mariko Carey was supported by a NHMRC TRIP Fellowship (APP1073031). Dr Allison Boyes was supported by a NHMRC Early Career Fellowship (APP1073317) and Cancer Institute NSW Early Career Fellowship (13/ECF/1-37).

Conflicts of Interest

The authors declare no conflicts of interest directly or indirectly relating to this research.

Informed Consent

Ethical approval was granted by the Ethics Committees of each of the hospitals in this study, and all procedures performed involving human participants were in accordance with the ethical standards of the institutional research committee and with the1964 Declaration of Helsinki and its later amendments, Written informed consent was obtained from all individual participants included in the study.