Remote, proactive, telephone based management of toxicity in outpatients during adjuvant or neoadjuvant chemotherapy for early stage breast cancer: pragmatic, cluster randomised trial

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ABSTRACT

OBJECTIVE

To evaluate the effectiveness of remote proactive management of toxicities during chemotherapy for early stage breast cancer.

DESIGN

Pragmatic, cluster randomised trial.

SETTING

20 cancer centres in Ontario, Canada, allocated by covariate constrained randomisation to remote management of toxicities or routine care.

PARTICIPANTS

All patients starting adjuvant or neoadjuvant chemotherapy for early stage breast cancer at each centre. 25 patients from each centre completed patient reported outcome questionnaires.

INTERVENTIONS

Proactive, standardised, nurse led telephone management of common toxicities at two time points after each chemotherapy cycle.

MAIN OUTCOME MEASURES

The primary outcome, cluster level mean number of visits to the emergency department or admissions to hospital per patient during the whole course of chemotherapy treatment, was evaluated with routinely available administrative healthcare data. Secondary patient reported outcomes included toxicity, self-efficacy, and quality of life.

RESULTS

Baseline characteristics of participants were similar in the intervention (n=944) and control arms (n=1214); 22% were older than 65 years. Penetration (that is, the percentage of patients who received the intervention at each centre) was 50-86%. Mean number of visits to the emergency department or admissions to hospital per patient was 0.91 (standard deviation 0.28) in the intervention arm and 0.94 (0.40) in the control arm (P=0.94); 47% (1014 of 2158 patients) had at least one visit to the emergency department or a hospital admission during chemotherapy. Among 580 participants who completed the patient reported outcome questionnaires, at least one grade 3 toxicity was reported by 48% (134 of 278 patients) in the intervention arm and by 58% (163 of 283) in the control arm. No differences in self-efficacy, anxiety, or depression were found. Compared with baseline, the functional assessment of cancer therapy trial outcome index decreased by 6.1 and 9.0 points in the intervention and control participants, respectively.

CONCLUSIONS

Proactive, telephone based management of toxicities during chemotherapy did not result in fewer visits to the emergency department or hospital admissions. With the rapid rise in remote care because of the covid-19 pandemic, identifying scalable strategies for remote management of patients during cancer treatment is particularly relevant.

TRIAL REGISTRATION

ClinicalTrials.gov NCT02485678.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Visits to the emergency department and admissions to hospital are common during cancer chemotherapy

These visits might be preventable with adequate support between clinic visits, but large scale studies of remote management are limited

WHAT THIS STUDY ADDS

Proactive, telephone based management of toxicities during chemotherapy did not reduce the number of visits to the emergency department or admissions to hospital

With the rapid rise in remote care because of the covid-19 pandemic, identifying scalable strategies for remote management of patients during cancer treatment is particularly relevant

Introduction

Chemotherapy has an important role in the management of many cancers but is associated with significant toxicity. As chemotherapy is mostly administered in outpatient settings, toxicities related to chemotherapy occur between visits to the cancer centre. Population based studies suggest that the use of acute care is common during chemotherapy[1-3]; 42% of patients receiving systemic treatment in routine practice had at least one visit to the emergency department or an admission to hospital during treatment.[4] Many toxicities are predictable and can be prevented or improved with earlier intervention. Consequently, rates of use of acute care and patient outcomes could be better with effective proactive remote support between visits to the clinic.

Over the past decade, substantial interest has been seen in identifying approaches to support patients with cancer receiving chemotherapy between visits to the cancer centre, to minimise toxicity, improve quality of life, and reduce the use of acute care. Remote interventions, such as telephone based outreach[5 6] and mobile applications or devices,[7 8] have shown promise in early phase or proof of concept individually randomised studies. Although large scale evaluations are currently in progress,[9 10] data on the effectiveness and scalability of these types of interventions at a system level are limited. In our previous single arm two institution study of a proactive, telephone based outreach strategy which focused on the management of toxicity by trained oncology nurses in patients undergoing adjuvant chemotherapy for breast cancer, we showed that the intervention was feasible, acceptable to patients and providers, and associated with fewer visits to the emergency department compared with historical controls.[11] Here, we report the effectiveness of remote proactive management of toxicities related to chemotherapy in patients with early stage breast cancer receiving chemotherapy, in a multicentre, pragmatic, cluster randomised trial where the primary outcome was evaluated with existing administrative healthcare data. We also conducted a study of validated questionnaires in a subset of patients to evaluate the effect of the intervention on patient reported outcomes.

Methods

Study design

We conducted a pragmatic, cluster randomised trial to evaluate the effect of proactive, nurse led, telephone based management of symptoms on the cluster level number of visits to the emergency department or admissions to hospital per patient; the full trial protocol has been published previously.[12] Briefly, 20 cancer centres in Ontario, Canada, were randomly allocated to proactive remote management (intervention, n=10) or routine care (control, n=10), grouped by the size of the centre (large, medium, or small, based on historical numbers of patients with breast cancer). Participants had early stage (stages I-III) breast cancer and were starting adjuvant or neoadjuvant chemotherapy at participating institutions during the intervention period. Excluded were patients receiving an investigational drug or treated exclusively with hormonal or targeted treatments.

Ethical considerations

The intervention was introduced into the centres as a process change according to quality improvement principles, and therefore individual written informed consent was waived.[13] Informed consent was also waived for control centres providing their local standard of care. The subset of patients participating in the patient reported outcomes sub-study were asked to provide individual written informed consent to participate and for linkage of their patient reported outcome data to provincial administrative data.

Intervention arm

The cluster randomisation was performed at the Ontario Clinical Oncology Group, Hamilton, Ontario, with population based administrative healthcare data to determine historical patient volumes, number of visits to acute care facilities, Charlson comorbidity index, urban versus rural geographical location, stage of cancer, chemotherapy regimen, type of facility, and centre surveys to determine the nursing model and the proportion of non-English speaking patients. Centres randomised to the intervention arm offered the proactive telephone symptom management programme to all eligible patients starting adjuvant or neoadjuvant chemotherapy for early stage breast cancer during the enrolment period.

Participants in the intervention arm received a copy of the Symptom Self-Management Booklet-patient edition (supplementary file 1) and two structured follow-up calls during each cycle of chemotherapy: 24-72 hours and 8-10 days after the start of each cycle (supplementary figure 1). During the calls, symptoms were assessed by locally designated oncology nurses with a standardised questionnaire (supplementary file 2), looking at nine common toxicities related to chemotherapy: nausea, vomiting, mouth and throat sores, pain, aching joints and aching muscles, loose and watery stools, shivering or shaking chills, constipation, and fatigue or tiredness. Standardised guidance of the management of symptoms was provided by the Symptom Self-Management Booklet-provider edition (supplementary file 3) and the telephone follow-up script (supplementary file 4). The care team made unscheduled calls to follow-up on symptoms or to provide more support at their discretion.

Control arm

Participants in the control centres received standard care according to their institution. Typically, standard care involved baseline patient education on chemotherapy and common side effects, and advice to call the cancer centre about symptoms or concerns related to the treatment between visits to the clinic.

Primary outcome

The primary outcome was the cluster level mean number of visits to the emergency department or admissions to hospital per patient during the at-risk period, defined as the chemotherapy treatment period from the first day of the first cycle of chemotherapy to 30 days after the last chemotherapy treatment. The primary outcome was measured with administrative healthcare data from Ontario. Ontario has a single payer universal healthcare system with a comprehensive population based cancer registry capturing diagnostic and demographic information on about 98% of patients.[14] All patients with breast cancer at the participating centres who started adjuvant or neoadjuvant chemotherapy during the intervention period were identified from the provincial activity level reporting database, which includes information on drugs received, dates of

treatment, and the institution where the treatment was given. The Ontario Cancer Registry was used to confirm that the patient had early stage breast cancer. The National Ambulatory Care Reporting System and Canadian Institutes for Health Information Discharge Abstract Database are comprehensive databases that capture all visits to the emergency department and admissions to hospital, respectively, at any hospital in Ontario; details of this methodology have been described previously.[1] Briefly, all unique visits to the emergency department and admissions to hospital during the at-risk period were identified and added for each patient. Visits to the emergency department that led to admission to hospital were counted as one acute care episode.

Secondary outcomes

Implementation fidelity (the degree to which an intervention is delivered as intended) was assessed based on the core elements of Carrol et al.[15] Adherence was defined as completion of 80% of the expected telephone calls on managing toxicities related to chemotherapy (patient reached and counselling provided) within the call window specified by the protocol. Penetration was defined as the proportion of patients who received the intervention at the 10 intervention sites out of those eligible, which was determined from the administrative healthcare data.

After a run-in period of one month following the start of the study, the centres were instructed to approach consecutive eligible patient to participate in the patient reported outcomes study until the recruitment target of at least 25 patients per centre (500 overall) was reached. Participants completed the validated patient reported outcome questionnaires before the start of the first (visit 1, baseline) and second (visit 2) cycles of chemotherapy, and within 60 days of the end of treatment (visit 3). Participants who received a chemotherapy regimen where they switched to a different drug part way through their treatment (usually a taxane was added) completed another patient reported outcome questionnaire before the start of the second cycle of the second drug (visit 2a). The severity of the toxicities related to chemotherapy was measured[16 17] and scored[18] with the National Cancer Institute patient reported outcomes version of the common terminology criteria for adverse events (NCI PRO-CTCAE) self-report tool. Self-efficacy or confidence in managing symptoms was measured with the Stanford self-management self-efficacy scale,[19] and general quality of life by the EQ-5D-3L (three level version of the European quality-of-life five dimension instrument).[20] The patient health questionnaire 9[21] and generalised anxiety disorder 7[22] scales measured major depression and anxiety, respectively. Physical, social, and family wellbeing were measured with the functional assessment of cancer therapy for patients with breast cancer (FACT-B) scales.[23] Coordination and continuity of care was evaluated with the adapted Picker survey.[24 25]

Statistical analysis

For the primary outcome, we conducted two different simulation approaches to determine sample size: (1) assuming an over disperse Poisson model (negative binomial distribution) for the number of visits to the emergency department or admissions to hospital, and with summary data from an a prior population based cohort of patients with breast cancer, we selected the top 25 cancer treatment centres in Ontario by patient volume to maintain estimate stability; and (2) with the actual data from the cohort and randomly allocating the 20 largest centres equally to a control or treatment arm within five groups, based on the number of patients with breast cancer treated at each centre. With the first model based approach, we applied a design effect to the number calculated assuming independence. The intraclass correlation for the top 25 cohort was estimated at 0.028. In the second actual data approach, we reduced the observed visits by a fixed prespecified percentage, ranging from 20% to 40%. Both approaches resulted in similar estimates. About 73 women per centre (total sample size=1460) from 20 centres were needed to achieve 80% power to detect a 33% reduction in the number of visits to the emergency department or admissions to hospital, with a one sided α value of 2.5%. For the patient reported outcomes study, at least 25 participants per centre (total sample size=500) were needed for 80% power (one sided α value of 2.5%) to detect a treatment effect size of 0.35 standard deviations, with adjustment for clustering (intraclass correlation=0.028) and an allowance of 3% for non-compliance.

We used descriptive statistics to summarise the characteristics of the full study cohort and the patient reported outcomes study cohort. Aggregated diagnosis group was derived from the Johns Hopkins Adjusted Clinical Groups System[26] as a validated measure of the complexity of comorbidities and the consumption of resources. The effect of the intervention on the unweighted centre level mean number of visits to the emergency department or admissions to hospital per patient was calculated for both the size of the centre (small, medium, or large) and overall, for the intervention and control arms, and compared using t scores (evaluated with only the 2890 acceptable permutations of the 20 centres after applying covariate based restrictions) and the permutation test. Confidence intervals were calculated by bootstrapping. Supplementary file 5 gives details of the analysis, including a supportive analysis with patient level data and a sensitivity analysis.

Patient reported outcomes (secondary outcomes) were measured at the patient level. The worst grade (grade 3) toxicities reported after baseline, based on the NCI PRO-CTCAE, were summarised for the intervention and control arms and compared with a mixed effects logistic model adjusting for fixed effects (baseline toxicity score, intervention, and size of the centre) and centre as a random effect. Correlations for different patients within the same cluster were taken

into account in the model, and a general unstructured covariance model was assumed. The effect of the intervention on the quality of life patient reported outcome measures was evaluated with linear mixed models for repeated measures (fixed effects included the baseline quality of life score, intervention, visit, intervention-by-visit interaction, and size of the centre; random effects were centres, with an unstructured covariance matrix for visits and the clustering of the individuals within centres). All analyses were conducted with SAS 9.4 and R 3.5 on the Institute for Clinical Evaluative Sciences data and analytic virtual environment secure server.

Patient and public involvement

At the time that this study was first conceptualised, including patients as research team members was not usual practice in Canada and hence patients were not formally involved in the research process. However, we did seek consultation on the study concept with patients at multiple time points throughout the research process. The proposal was presented at Cancer Care Ontario, the provincial body overseeing cancer care, for feedback and engagement, with patient partner involvement on several occasions. Also, our previous pilot study[11] involved the collection of patient satisfaction measures and extensive end-of-study patient interviews on the intervention content and delivery, which informed the design of this trial.

Results

Cohort description

During the enrolment period from February 2016 to November 2017, 2158 patients started adjuvant or neoadjuvant chemotherapy for early stage breast cancer at the 20 participating institutions (fig 1). Baseline characteristics (table 1) were similar in the intervention (n=944) and control arms (n=1214). Median age was 55, and most participants had stage 2 disease. The most commonly used regimens were AC-paclitaxel (doxorubicin (Adriamycin) and cyclophosphamide, followed by paclitaxel) and FEC-docetaxel (5-fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel). Baseline characteristics for the 580 patients (27% of the main cohort) who participated in the patient reported outcomes study were similar to those of the main cohort (table 1).

Intervention delivery characteristics

The number of participants who received the intervention varied by cancer centre (range 44-141 patients; supplementary table 1). The overall intervention penetration at centres randomised to the intervention arm was 68% (range over 10 centres 50-86%). Of the 7940 expected proactive calls, 78% were completed (range 60-95%), of which 84% were completed within the time window (range 68-97%). We found no trend between centre size and the proportion of calls delivered; 347 unscheduled calls were made at the discretion of the intervention nurses over the

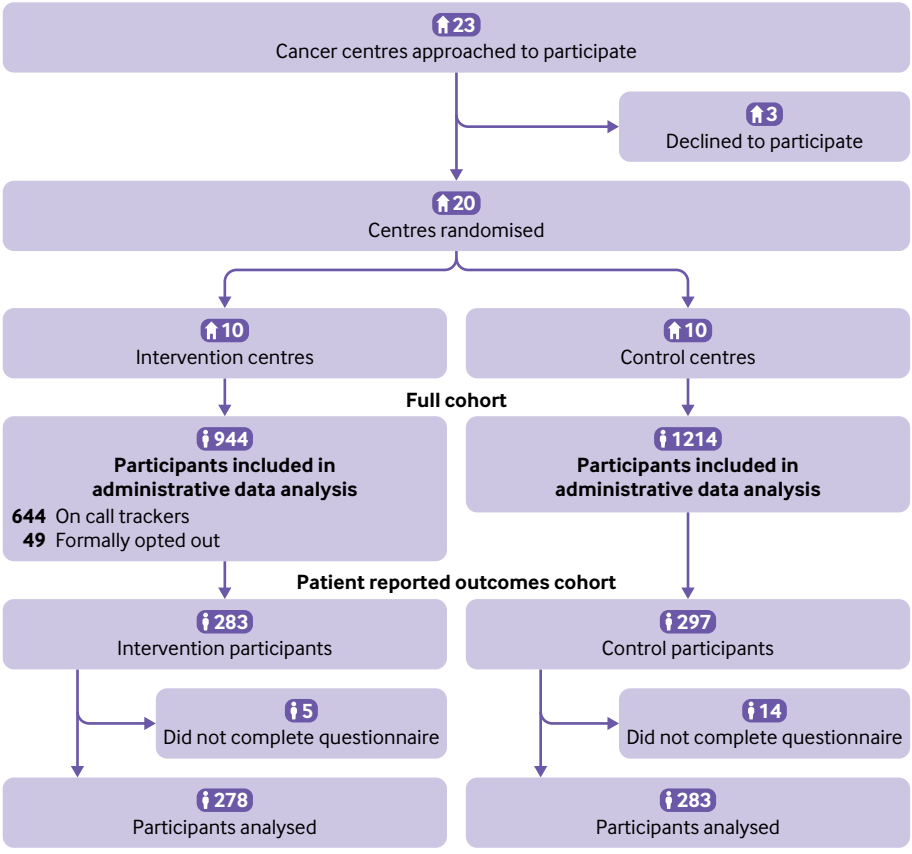

Fig 1 | CONSORT (Consolidated Standards of Reporting Trials) diagram

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Table 1 | Characteristics of full cohort and patient reported outcomes cohort. Data are number (%) of participants unless stated otherwise

	Full cohort (n=2158)		Patient reported outcomes cohort (n=580)	
Characteristic	Intervention (n=944)	Control (n=1214)	Intervention (n=283)	Control (n=297)
Age (years)*				
<40	86 (9)	99 (8)	31 (11)	25 (8)
40-44	84 (9)	99 (8)	26 (9)	22 (7)
45-49	117 (12)	173 (14)	42 (15)	47 (16)
50-54	171 (18)	212 (17)	44 (16)	62 (21)
55-59	128 (14)	209 (17)	38 (13)	56 (19)
60-64	135 (14)	170 (14)	45 (16)	42 (14)
65-69	117 (12)	128 (11)	39 (14)	25 (8)
70-74	61 (6)	74 (6)	12 (5)	12 (4)
≥75	45 (5)	50 (4)	6 (2)	6 (2)
Stage				
I	215 (23)	232 (20)	63 (22)	61 (21)
IIA	264 (28)	334 (28)	82 (29)	90 (30)
IIB	216 (23)	299 (25)	67 (24)	68 (23)
IIIA	139 (15)	215 (18)	44 (16)	57 (19)
IIIB	44 (5)	57 (5)	9 (3)	8 (3)
IIIC	42 (4)	51 (4)	9 (3)	7 (2)
IV	<6 (NR)	<6 (NR)	<6 (NR)	<6 (NR)
Unknown	22 (2)	23 (2)	<6 (NR)	<6 (NR)
Chemotherapy				
Regimen:				
AC-P	417 (44)	539 (44)	118 (42)	139 (47)
FEC-D	234 (25)	331 (27)	80 (28)	86 (29)
TC	201 (21)	182 (15)	58 (20)	46 (15)
AC-Doc	8 (1)	36 (3)	<6 (NR)	<6 (NR)
Other	84 (9)	126 (10)	25 (9)	23 (8)
Class:†				
Anthracycline	664 (70)	945 (78)	202 (71)	234 (79)
Docetaxel	478 (51)	575 (47)	156 (55)	141 (47)
Paclitaxel	456 (48)	583 (48)	124 (44)	149 (50)
Charlson score				
0	226 (24)	336 (28)	60 (21)	74 (25)
1	35 (4)	54 (4)	10 (4)	7 (2)
≥2	20 (2)	14 (1)	<6 (NR)	<6 (NR)
Unknown	663 (70)	810 (67)	209 (74)	213 (72)
Income group				
1	148 (16)	180 (15)	40 (14)	34 (11)
2	184 (19)	215 (18)	54 (19)	40 (14)
3	191 (20)	255 (21)	58 (20)	55 (19)
4	186 (20)	268 (22)	61 (22)	85 (29)
5	234 (25)	292 (24)	70 (25)	80 (27)
ADG total				
0-4	171 (18)	211 (18)	50 (18)	60 (20)
5-9	527 (56)	682 (56)	160 (56)	172 (58)
≥10	246 (26)	321 (26)	73 (26)	65 (22)
Mean (range)	7.6 (0-20)	7.5 (0-25)	7.6 (1-20)	7.1 (0-23)
Rural				
Yes	79 (8)	116 (9)	27 (10)	34 (11)
No	864 (92)	1094 (90)	256 (90)	260 (88)

AC-P=doxorubicin (Adriamycin), cyclophosphamide, paclitaxel; FEC-D=fluorouracil, epirubicin, cyclophosphamide, docetaxel; TC=docetaxel, cyclophosphamide; AC-Doc=doxorubicin (Adriamycin), cyclophosphamide, docetaxel; ADG=aggregated diagnostic group; NR=not reported because counts were <6 (Institute for Clinical Evaluative Sciences where analyses were performed does not allow reporting of cells with <6 patients).
*Median age is 55.7 (estimated from grouped data).
†Patients might fit into more than one category.

course of delivering the intervention, and the number of completed extra calls varied by centre (range 1-115).

Effect of intervention on visits to the emergency department and admissions to hospital

Overall, 47% (1014 of 2158 patients) of patients had at least one visit to the emergency department or admission to hospital during treatment. Figure 2 shows the distribution of visits to the emergency department or admissions to hospital by the size of the centre (large, medium, or small) and overall (supplementary table 2 shows individual centre data). Large control centres and small intervention centres had fewer visits to the emergency department or admissions to hospital (supplementary table 3). Based on the centre level mean number of visits to the emergency department or admissions to hospital, we found no significant difference between the intervention (0.91, standard deviation 0.28) and control (0.94, 0.40) groups, with a mean absolute difference of −0.024 (95%

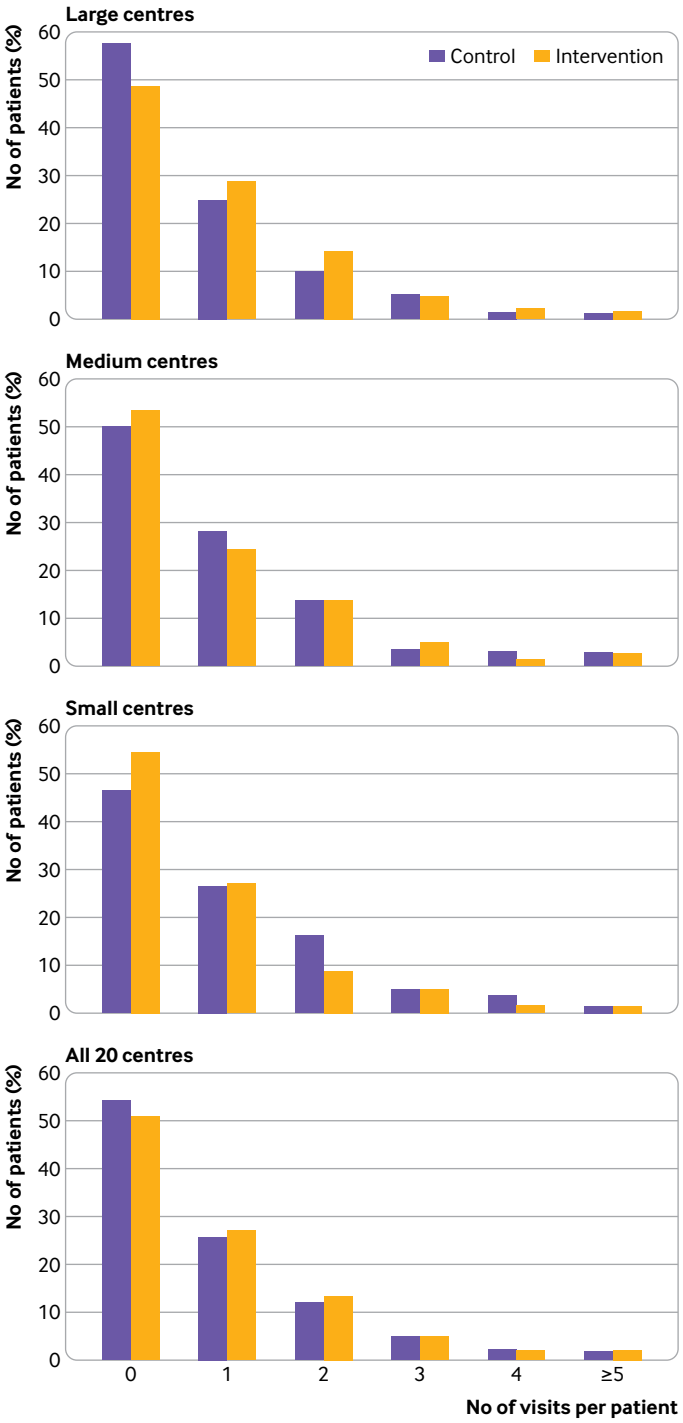

Fig 2 | Distribution of visits to the emergency department or admissions to hospital per patient by size of centre and overall

confidence interval −0.24 to 0.15, P=0.85) (table 2). The intraclass correlation for the primary outcome was 0.018 versus 0.028, which was used in our sample size calculations. A covariate adjusted supportive analysis and a sensitivity analysis did not affect the results (supplementary file 5). Also, we found no cluster level differences between the intervention and control arms for visits to the emergency department alone (mean absolute difference −0.010, 95% confidence interval −0.216 to 0.145, P=0.92) or admissions to hospital (−0.014, −0.064 to 0.035, P=0.67). Intervention penetration had no effect on the primary outcome.

Effect on patient reported outcomes

Twenty two participants in the patient reported outcomes study did not complete a questionnaire (five in the intervention arm and 14 in the control arm). At least one grade 3 toxicity was reported by 48% (134 of 278 patients) in the intervention arm and by 58% (163 of 283) in the control arm (P=0.0053, table 3). Substantial differences were observed between the intervention and control arms in the proportion of patients experiencing grade 3 fatigue (58 of 278 patients (21%) *v* 90 of 283 (32%)), aching joints (61 (22%) *v* 84 (30%) patients), and aching muscles (53 (19%) *v* 77 (27%) patients). Supplementary table 4 gives a more detailed analysis of the toxicity grade during follow-up. We found no effect of the intervention on anxiety (generalised anxiety disorder 7) or depression (patient health questionnaire 9) (table 4). We also found no improvement in self-efficacy (Stanford self-management self-efficacy scale) or coordination of care (adapted Picker survey) in patients receiving the intervention. During the at-risk period, patients in the intervention group had a smaller decline from baseline for the functional assessment of cancer therapy (FACT) trial outcome index (−6.1 *v* −9.0, difference 2.9, 95% confidence interval 0.8 to 5.0) and FACT physical wellbeing (−3.0 *v* −4.6, 1.6, 0.7 to 2.5).

Discussion

Principal findings

Over the past decade, there has been substantial interest in identifying effective approaches to support patients with cancer remotely during chemotherapy, to minimise toxicity, improve quality of life, and reduce the use of acute care facilities. In our trial, we found that despite a high overall rate of use of acute care in this patient population (47% of patients had at least one visit to the emergency department or admission to hospital during treatment), proactive telephone management of toxicities related to chemotherapy of curative intent did not result in a decrease in the number of visits to the emergency department or admissions to hospital between the intervention and control centres. Failure to detect a difference could be because of suboptimal penetration (overall 68%, range 50-86%) or low intervention fidelity (78% of calls were completed, centre range 60-95%), or both, diluting any potential observable effect, although we did not see a strong correlation between penetration and visits to the emergency department or admissions to hospital. Unfortunately, complex interventions that show early promise but then fail to translate to substantial differences in outcomes after large scale implementation is not unusual.[27] Furthermore, proactive support might have directed patients to the emergency department who would otherwise not have sought care because some of the nursing algorithms advise patients to go to the emergency department if

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Table 2 | Unweighted centre level mean number of visits to the emergency department or admissions to hospital per patient by size of centre during the at-risk period*

Size of centre	Intervention		Control		Mean difference (95% CI) between intervention and control
	No of patients (centres)	Mean (SD)	No of patients (centres)	Mean (SD)	
Large	532 (5)	0.90 (0.07)	778 (5)	0.74 (0.17)	0.17 (−0.05 to 0.38)
Medium	302 (3)	0.92 (0.23)	216 (2)	0.97 (0.16)	−0.04 (−0.60 to 0.51)
Small	110 (2)	0.92 (0.76)	220 (3)	1.25 (0.63)	−0.33 (−3.25 to 2.58)
Overall	944 (10)	0.91 (0.28)	1214 (10)	0.94 (0.40)	−0.024 (−0.24 to 0.15)†

SD=standard deviation.
*From the start of chemotherapy to the end plus 30 days.
†Cluster level overall group comparison P=0.85 based on permutation test (when adjusted for size of centre P=0.94); confidence intervals calculated by bootstrapping.

no other avenues for urgent evaluation are available, which was the case for most participating centres during the study. Also, lack of effect could be caused by temporal changes in supportive care during cancer treatment across Ontario during the study period because improving the management of toxicities for patients with cancer receiving systemic treatment was a provincial priority.[28-30] Hence some of the control centres might have introduced interventions in their centres to improve patient support during treatment, such as establishment of urgent care clinics.[31]

Comparison with other studies

Our intervention was associated with a lower proportion of patients with grade 3 toxicities (P=0.05), especially fatigue (P=0.009), aching joints (P=0.003), and aching muscles (P=0.004), and significant findings for quality of life outcomes that did not fully meet the criteria for a clinically important difference.[32] These findings are similar to previous studies, which showed that proactive remote monitoring of symptoms during cancer treatment is associated with a positive effect on symptoms and quality of life[8 33 34] and suggests that the effect on symptom burden might be scalable beyond individually randomised trials. In contrast with physical symptoms, our intervention was not associated with improvements in other patient reported outcomes, such as self-efficacy, anxiety, or depression. Lack of effect on self-efficacy could be because of high baseline scores and a possible ceiling effect, and a focus on the management of symptoms rather than teaching self-management behaviours. A recent single centre trial of remote electronic monitoring coupled with self-management training during chemotherapy reported improved self-efficacy in the intervention arm.[34] Lack of effect on anxiety or depression might be because of the content of the calls, which focused on physical rather than emotional symptoms.

Strengths and limitations

This study had several unique design aspects: cluster randomisation, introduction of the intervention as a process change according to quality improvement principles at each intervention centre, a pragmatic approach that mimicked implementation in routine practice, and the use of existing population based administrative healthcare data to evaluate the primary outcome. Substantial interest in the use of routinely collected healthcare data to improve clinical trials by decreasing costs and burden has been reported,[27] although a recent systematic review suggested that such trials might show smaller treatment effects than traditional trials.[35] We showed that use of routinely collected administrative data to evaluate trial outcomes is feasible. Use of administrative data in our study facilitated the recruitment of smaller community centres into our trial; extensive collection of primary data could have been a barrier to participation for these smaller centres. Furthermore, for outcomes such as use of healthcare services, administrative data might be more accurate than patients' own reports.

The study had some limitations. We conducted a covariate constrained randomisation to minimise imbalance between the intervention and control arms

Table 3 | Summary of grade 3 toxicity by group and type based on responses to National Cancer Institute patient reported outcomes version of common terminology criteria for adverse events questionnaire*

Toxicity type	No of patients with any grade 3 toxicity (% of group))		P value†
	Intervention (n=278)	Control (n=283)	
Fatigue, tiredness, or lack of energy	58 (21)	90 (32)	0.009
Loose and watery stools, diarrhoea	11 (4)	<6 (NR)	0.16
Nausea	23 (8)	24 (8)	0.54
Vomiting	<6 (NR)	<6 (NR)	0.52
Pain	85 (31)	100 (35)	0.15
Aching joints	61 (22)	84 (30)	0.003
Aching muscles	53 (19)	77 (27)	0.004
Constipation	26 (9)	39 (14)	0.18
Mouth and throat sores	11 (4)	12 (4)	0.97
Shivering or shaking chills	6 (2)	10 (4)	0.42
Any toxicity	134 (48)	163 (58)	0.005

NR=not reported (Institute for Clinical Evaluative Sciences does not allow reporting of table cells with <6 patients).
*Grade 3 toxicity at any visit after baseline based on composite scoring algorithm.[18]
†Based on a logistic mixed effects model with fixed effects (baseline toxicity score, intervention, size of centre group) and centre as a random effect. Correlations for different patients in the same cluster have been taken into account in the model; a general unstructured correlation was used.

Table 4 | Patient reported quality of life outcomes linear mixed model analysis for change from baseline

Scale*	Visit change	Intervention estimate (SE)	Control estimate (SE)	Difference estimate (95% CI)†	Overall effect (P value)‡	
					Visit	Intervention
Functional assessment for cancer therapy for patients with breast cancer (FACT-B):						
Trial outcome index	V2–V1	−2.4 (0.7)	−4.9 (0.6)	2.5 (0.7 to 4.3)	<0.001	0.004
	V2a–V1	−7.7 (0.8)	−9.6 (0.8)	2.0 (−0.2 to 4.2)		
	V3–V1	−6.1 (0.8)	−9.0 (0.8)	2.9 (0.8 to 5.0)		
Physical wellbeing	V2–V1	−2.4 (0.3)	−3.4 (0.3)	1.0 (0.2 to 1.9)	<0.001	0.001
	V2a–V1	−4.3 (0.4)	−5.3 (0.3)	1.0 (0.0 to 2.0)		
	V3–V1	−3.0 (0.3)	−4.6 (0.3)	1.6 (0.7 to 2.5)		
Social wellbeing	V2–V1	0.0 (0.2)	−0.3 (0.2)	0.3 (−0.3 to 0.9)	<0.001	0.51
	V2a–V1	−0.5 (0.3)	−0.6 (0.2)	0.1 (−0.6 to 0.8)		
	V3–V1	−0.8 (0.2)	−0.9 (0.2)	0.1 (−0.6 to 0.8)		
Emotional wellbeing	V2–V1	1.4 (0.2)	1.4 (0.2)	0.0 (−0.4 to 0.4)	0.95	0.89
	V2a–V1	1.2 (0.2)	1.6 (0.2)	−0.3 (−0.9 to 0.2)		
	V3–V1	1.6 (0.2)	1.3 (0.2)	0.3 (−0.2 to 0.8)		
Functional wellbeing	V2–V1	−0.6 (0.3)	−1.5 (0.3)	0.8 (0.1 to 1.6)	<0.001	0.15
	V2a–V1	−2.8 (0.3)	−2.9 (0.3)	0.1 (−0.8 to 1.0)		
	V3–V1	−2.0 (0.3)	−2.5 (0.3)	0.5 (−0.3 to 1.4)		
EQ-5D-3L VAS	V2–V1	1.3 (0.8)	−0.8 (0.8)	2.1 (−0.1 to 4.2)	<0.001	0.031
	V2a–V1	−2.4 (1.1)	−5.8 (1.1)	3.4 (0.4 to 6.4)		
	V3–V1	−3.6 (1.0)	−4.7 (1.0)	1.1 (−1.6 to 3.8)		
Stanford	V2–V1	0.3 (0.1)	0.3 (0.1)	0.0 (−0.3 to 0.3)	0.009	0.57
	V2a–V1	0.2 (0.1)	−0.1 (0.1)	0.2 (−0.1 to 0.6)		
	V3–V1	0.3 (0.1)	0.3 (0.1)	0.0 (−0.3 to 0.3)		
Picker (adapted)	V2–V1	6.0 (1.4)	4.0 (1.4)	2.0 (−2.0 to 5.9)	0.093	0.67
	V2a–V1	7.0 (1.8)	7.1 (1.7)	−0.1 (−5.1 to 4.9)		
	V3–V1	4.6 (1.6)	4.2 (1.5)	0.4 (−3.9 to 4.7)		
GAD-7	V2–V1	−2.1 (0.2)	−2.1 (0.2)	0.0 (−0.5 to 0.6)	0.91	0.59
	V2a–V1	−2.4 (0.2)	−2.0 (0.2)	−0.5 (−1.2 to 0.2)		
	V3–V1	−2.1 (0.2)	−2.2 (0.2)	0.1 (−0.6 to 0.7)		
PHQ-9	V2–V1	0.3 (0.2)	0.7 (0.2)	−0.4 (−1.0 to 0.2)	<0.001	0.07
	V2a–V1	1.2 (0.3)	1.7 (0.3)	−0.5 (−1.2 to 0.3)		
	V3–V1	0.6 (0.2)	1.0 (0.2)	−0.5 (−1.1 to 0.2)		

SE=standard error; V1=baseline; V2=before start of second cycle; V2a=before start of second cycle of a taxane (if they switched regimens); V3=within 60 days of the end of chemotherapy; PHQ-9=patient health questionnaire 9; EQ-5D-3L VAS=three level version of the European quality of life five dimension visual analogue scale; GAD-7=generalised anxiety disorder 7; Stanford=Stanford self-management self-efficacy scale.
*Score ranges for instruments: FACT-B total score (0-148); EQ-5D-3L VAS (0-100); Picker (adapted) (0-100); Stanford (1-10); GAD-7 (0-21); PHQ-9 (0-27).
†Estimates of positive differences for FACT-B, EQ-5D-3L VAS, Stanford, and Picker scales, and negative differences for GAD and PHQ, suggest less decline for patients at the intervention centres
‡With general linear mixed modelling, the predictors are considered to have a fixed or random effect. Fixed effects include baseline score, intervention, visit, intervention-visit interaction, and size of centre group; centre is a random effect. Correlations for different patients in the same cluster and for different visits from the same patient have also been taken into account in the model. No interaction terms were found to be significant (P<0.05).

based on the primary outcome. The patient reported outcome endpoints were prespecified as secondary outcomes, but the patient reported outcomes study did not account for multiple comparisons and therefore we chose the conservative approach and considered them exploratory. Also, the patient reported outcome questionnaires were completed by 580 patients, a subset of the total study population (27%), who might not have been representative of the full cohort. The study protocol specified an interval between accrual for the study (February 2016 to November 2017) and reporting of the findings, to allow for completion of the toxicity observation window and for the updated administrative data holdings covering the study period to become available from the Institute for Clinical Evaluative Sciences (updated annually for some databases). Administrative data lack the clinical contextual information required to understand the appropriateness of care or potential drivers of observed outcomes, such as patient preferences or unmeasured confounders.[36] Also, the study was conducted in Ontario, Canada, which has a universal single payer system, so administrative records capture the complete care episode consistently and completely for patients with cancer.[37] Issues might arise operating a similar methodology in multipayer systems. Lastly, extra unscheduled calls were made in the intervention arm, which might increase the resources required to deliver the intervention and should be considered in the design of future studies.

Conclusions

Remote, proactive, telephone based management of toxicities during chemotherapy did not result in fewer visits to the emergency department or admissions to hospital in this multicentre cluster randomised trial. Given the high level of acceptability of the intervention by patients[11] and providers,[38] and with a growing body of evidence from other studies showing the benefits of remote monitoring during chemotherapy,[7 8 33 34] future studies of proactive remote management should focus on pragmatic large scale implementation in routine care settings. Although implementation issues with evaluations of large scale programmes persist, with the rapid rise in remote care because of the covid-19 pandemic, identifying scalable strategies for remote support of patients during cancer treatment is particularly relevant, including telephone based

interventions, as this remains an important method for delivery of virtual care.[39] Because of the resource implications of large scale implementation of such programmes, provision of proactive monitoring during cancer treatment to high risk patients (those receiving certain regimens) or high risk situations (at the beginning of chemotherapy or in advanced disease),[7 40] might facilitate widespread adoption and should be prioritised for study.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Ontario Institute for Cancer Research (OICR) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; CCE and EG hold appointments at the OICR Health Services Research Programme; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the Ontario Cancer Research Ethics Board, a centralised ethics board used by 18 of the participating cancer centres (15-041), the Sault Area Hospital Research Ethics Board, and the Rouge Valley Health System Research Ethics Board.

Data sharing: Relevant anonymised patient level data available on reasonable request.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: How best to disseminate the trial findings was studied through interviews with key stakeholder groups, such as physicians, nurses, and management, after completion of the trial. This also involved studying potential facilitators and barriers to implementation, should the results warrant. We found wide support for the trial from most stakeholders. All stakeholders identify evidence of effectiveness as a key facilitating factor. However, as the primary outcome of the trial was negative, we will work in consultation with the quality improvement programme at the Ontario provincial cancer agency to agree key messaging to stakeholders. The results will be presented in a debriefing session with all participating cancer centres. Nationally, the results will be presented at the Canadian Cancer Research Conference. Internationally, the results have already been presented virtually at the European Society for Medical Oncology annual congress, September 2020.

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Web appendix: Supplementary tables and figures
Web appendix 1: Supplementary file 1—Symptom Management Guide for Early Stage Breast Cancer Patients receiving Adjuvant and Neoadjuvant Chemotherapy, Patient Version
Web appendix 2: Supplementary file 2—AToM telephone follow-up form
Web appendix 3: Supplementary file 3— Symptom Management Guide for Early Stage Breast Cancer Patients receiving Adjuvant and Neoadjuvant Chemotherapy, Provider Version
Web appendix 4: Supplementary file 4—Telephone Script- Follow-Up Calls
Web appendix 5: Supplementary file 5—Details of the Analysis of the Primary Outcome