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ORIGINAL ARTICLE

A pilot study: dose adaptation of capecitabine using mobile phone toxicity monitoring — supporting patients in their homes

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Abstract
Purpose Real-time symptom monitoring using a mobile phone is potentially advantageous for patients receiving oral chemotherapy. We therefore conducted a pilot study of patient dose adaptation using mobile phone monitoring of specific symptoms to investigate relative dose intensity of capecitabine, level of toxicity and perceived supportive care.
Methods Patients with breast or colorectal cancer receiving capecitabine completed a symptom, temperature and dose diary twice a day using a mobile phone application. This information was encrypted and automatically transmitted in real time to a secure server, with moderate levels of toxicity automatically prompting self-care symptom management messages on the screen of the patient's mobile phone or in severe cases, a call from a specialist nurse to advise on care according to an agreed protocol.
Results Patients (n=26) completed the mobile phone diary on 92.6 % of occasions. Twelve patients had a maximum toxicity grade of 3 (46.2 %). The average dose intensity for all patients as a percentage of standard dose was 90 %. In eight patients, the dose of capecitabine was reduced, and in eight patients, the dose of capecitabine was increased. Patients and healthcare professionals involved felt reassured by the novel monitoring system, in particular, during out of hours.
Conclusion It is possible to optimise the individual dose of oral chemotherapy safely including dose increase and to manage chemotherapy side effects effectively using real-time mobile phone monitoring of toxicity parameters entered by the patient.

Keywords Chemotherapy · Dose decrease · Dose increase · Managing side effects · Mobile phone technology

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Introduction

It is well recognised that cytotoxic chemotherapy may have significant side effects for the patient resulting in a reduced dose intensity [1]. Unlike intravenous treatments, the dose of oral chemotherapy may be adapted according to the side effects experienced whilst taking the course of tablets. However, reduction in chemotherapy dose intensity may compromise disease control and survival in patients with curable malignancies [2–4], whilst dose-dense schedules of chemotherapy may increase the proportion of patients surviving for 5 years or more [5]. A growing number of patients can be supported to self-manage, with remote monitoring and timely reaccess to the healthcare system, initiated either by patient or professional, and are encouraged to take as much responsibility for their health and well-being as possible [6]. This pilot study was therefore designed to explore dose adaptation of oral capecitabine, based on patient reported side effects and

symptoms via the use of a mobile phone with a preloaded application. Patient and healthcare professional perspectives of the system were gathered. The symptom diary was automatically transmitted by the mobile phone to a secure web server every time a diary was completed. The application provided individualised real-time feedback with self-help advice. Dose decrease was made real time and dose increase was considered at the subsequent clinic visit, both based on the review of this electronic diary information stored on the patient's web page.

Methods

Study design

The Dose Adaptation of Capecitabine Using Mobile Phone Toxicity Monitoring (DATACAP) study was a pilot, one arm, single-centre clinical study.

The study was approved by the NRES Ethics Committee South Central, Oxford A, sponsored by the University of Oxford, and managed and monitored by the Oncology Clinical Trials Office (OCTO). Patients gave written informed consent for participation in the trial. The software application was developed at the University of Oxford, and the mobile phones were programmed by t+ Medical (now OBS Medical, Abingdon, UK), who also supplied the server infrastructure.

Eligible patients were ≥18 years of age with metastatic colorectal or breast cancer commencing treatment on one of three specified regimens. Patients were required to be fit to start at full (100 %) starting dose of all drugs; to be able and willing to use a mobile phone; to have adequate renal, liver and bone marrow function; to have no obvious contraindications for study drugs; and to be able to read and understand English.

Patients with metastatic colorectal cancer were treated with capecitabine plus oxaliplatin (CAPOX) or capecitabine alone and appropriate patients with metastatic breast cancer were treated with capecitabine alone. Doses of capecitabine were calculated according to body surface area (BSA) with daily starting doses for colorectal cancer patients receiving CAPOX being 2,000 mg/m^2. Single-agent capecitabine was started at 2,500 mg/m^2 in patients with colorectal cancer and 2,000 mg/m^2 in patients with breast cancer. The dose of capecitabine was capped at a maximum BSA of 2 m^2 for phase 1 of the study, but subsequently changed to 2.2 m^2 on review of phase I results. The planned treatment regimen was eight 3-week cycles, with capecitabine taken twice daily for 2 weeks followed by a capecitabine-free week.

Implementation

At their first chemotherapy visit, each patient was given a Sony Ericsson c510 or a Nokia 6303c mobile phone preloaded with a custom application and shown how to use it. Patients were asked to use the phone application twice daily (morning and evening) to fill out a short diary containing entries for temperature, diarrhoea and assessments for vomiting, nausea, mucositis, hand–foot syndrome and for patients receiving oxaliplatin, peripheral neuropathy. The diary was based on the CTCAE (Version 3.0) grades, written in patient-friendly language as used in our previous study [7]. All patient entered data were encrypted and automatically transmitted in real time to a secure server (Fig. 1). Self-care advice was displayed on the phone screen when appropriate (e.g. a reminder to take loperamide for diarrhoea), and the number of capecitabine tablets to be taken was displayed followed by a prompt for the patients to confirm how many tablets had been taken (Fig. 2).

Patients recording grade 2 toxicity generated an amber alert. Red alerts were generated as a result of severe toxic side effects or prolonged moderate side effects (Table 1). Alerts were also generated when patients failed to submit symptoms via their phone for prolonged periods of time. A specialist nurse was available 24 h per day to provide clinical advice for severe toxicities; the study nurses monitored patients in work hours. During out of hours periods (evenings and at the weekends), the study pager was passed to an oncology nurse working on the ward and trained in the technology, in order to provide 24-h cover for the patients.

Capecitabine dose adaptations

Dose escalation was only permitted at the start of each new cycle of therapy, if diarrhoea toxicity had been no worse than grade 1 and if hand–foot syndrome, mucositis or vomiting had been no worse than grade 2 for a maximum of 2 days during the previous cycle. If dose reductions had previously been made, dose escalation was not permitted. A maximum of three increments were allowed (110, 120 and 130 % of the starting dose; Table 2). In contrast, dose reductions for capecitabine could be made in real time during a cycle or at the clinical assessment prior to starting a new cycle. Reductions were in increments of 15 % of the starting dose (to 85, 70 and 55 %) and if below 55 % was required the patient's chemotherapy was stopped (Table 3). Start of cycle dose reductions were based on clinical judgement.

A red alert relating to diarrhoea, mucositis, hand–foot syndrome or vomiting (triggered by a single grade 3 or 4 or prolonged grade 2 toxicity) resulted in the capecitabine treatment being interrupted until the patient had recovered, then recommenced at a reduced dose as outlined above. A patient was considered to have recovered when their reported symptoms were grade 1 or 0 for at least four consecutive diaries.

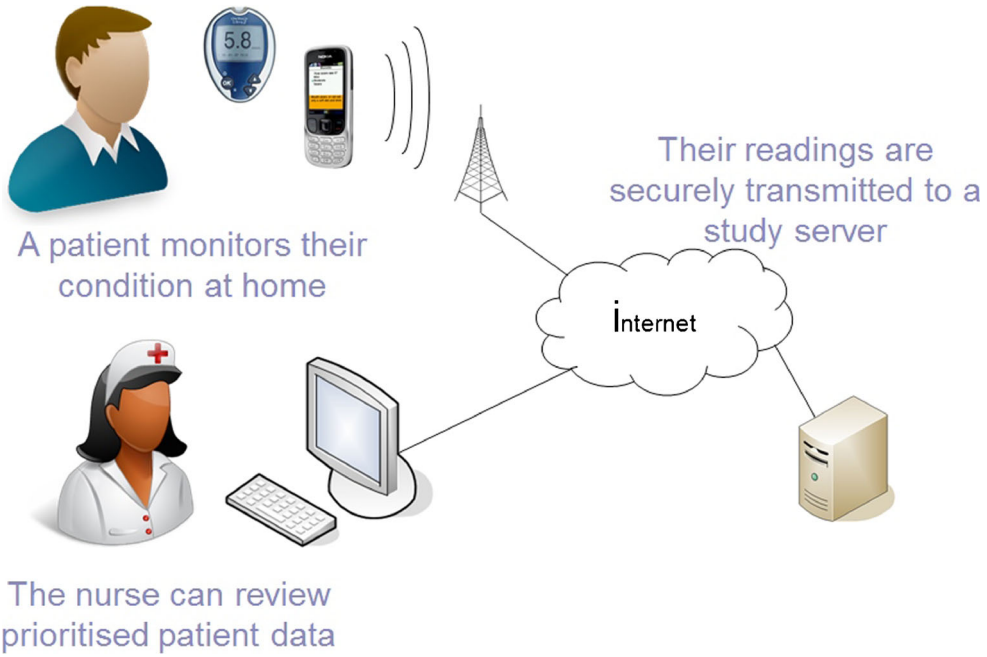

Fig. 1 Flowchart in monitoring patient's condition and sending mobile advice regarding self-care, medication and dosage

All dose changes, approved by the patient's oncologist, were logged on the system, which automatically updated the application on the patient's phone with the correct dose of capecitabine tablets for the next chemotherapy cycle.

All patients were invited to comment on the utility of mobile phone monitoring via a short interview with the nurse after their second cycle. The questions were based from the patient experience findings of the feasibility study [7] initiated with an open question on experience of using the system with probing of response, followed by six prompts on workability of system, involvement in care, response to symptoms, responsibility, confidence and other comments. Study nurses likewise were invited to state how they perceived the practicality of the study, at the end of recruitment. Comments from patients and staff were documented. A thematic analysis was undertaken for each group.

Statistical methods

The steering group developed the dose adaptation rules and subsequent algorithms de novo, led by the study statistician and based on standard dose banding of capecitabine based on patient's body surface area. The dose-adaptation algorithm had not previously been tested so we reassessed it and checked feasibility of the study design before expanding to more patients. The sample size for this pilot study was therefore computed in two phases. Under the standard dosing regimen, the expected distribution over all eight cycles of worst toxicities was one third of patients with at least grade 3. Based on this estimate, we specified phase I closing when at least six patients were recruited and three patients had demonstrated a dose increase. Dose reduction strategies were in lower increments than in other capecitabine trials. In phase I, there was two-weekly statistical monitoring and potential for

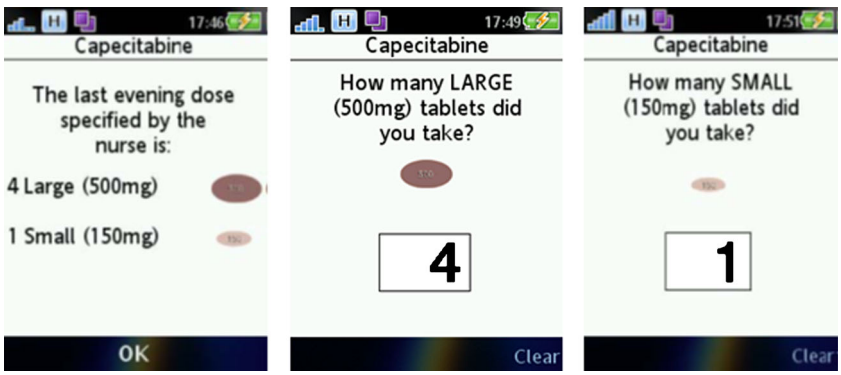

Fig. 2 Screen shots of medication advice as to capecitabine dosage followed by a prompt for the patients to confirm how many tablets had been taken

Table 1 Alerts

Severity	Condition	Parameter
Amber	Missed reading	No readings received in the last 14 h
	Borderline pyrexia with normal second reading	Reading in the range 37.5–37.9 °C and second reading (after 1 h) is <37.5 °C
	Moderate diarrhoea	Number of bowel movements over baseline in current reading≥2
	Moderate vomiting	Moderate vomiting in current reading
	Moderate nausea	Moderate nausea in current reading
	Moderate mucositis	Moderate mucositis in current reading
	Moderate hand–foot syndrome	Moderate hand–foot syndrome in current reading
	Moderate peripheral neuropathy	Moderate peripheral neuropathy in current reading
Red	No readings for previous day	No readings received in the last 30 h
	Incorrect capecitabine dose	Number of tablets taken, as entered by patient, differs from that specified on the website
	Borderline pyrexia and second reading not known	Borderline pyrexia where second reading is not taken within 90 min
	Borderline pyrexia lasting for an hour	Borderline pyrexia where second reading is also 37.5–37.9 °C
	Moderate diarrhoea lasting for 3 days	Number of bowel movements over baseline in each of the last six readings≥2
	Moderate mucositis lasting for 5 days	Moderate mucositis in all last ten readings
	Moderate vomiting lasting for 5 days	Moderate vomiting in all last ten readings
	Moderate hand–foot syndrome lasting for 5 days	Moderate hand–foot syndrome in all last ten readings
	Pyrexia	Current temperature reading is 38.0 °C or above
	Severe diarrhoea	Total number of bowel movements over baseline in current reading≥4
	Severe vomiting	Severe vomiting in current reading
	Severe nausea	Severe nausea in current reading
	Severe mucositis	Severe mucositis in current reading
	Severe hand–foot syndrome	Severe hand–foot syndrome in current readings
	Severe peripheral neuropathy	Severe peripheral neuropathy in current reading

algorithm changes. We considered 20 patients in phase II as sufficient to ascertain feasibility of the trial design and to provide estimates for powering a later, larger study. In phase II, monthly statistical monitoring was undertaken with no algorithm changes permitted. Thus, a minimum of 26 patients were needed in total. All patients received the mobile phone intervention.

Table 2 Dose escalation parameters

Symptom	Increase by 10 % if
Diarrhoea	Has been grade 1 or 0 for the previous cycle
Mucositis	Has been grade 1 or 0 for the previous cycle or grade 2 for a maximum of 2 days
Hand–foot syndrome	Has been grade 1 or 0 for the previous cycle or grade 2 for a maximum of 2 days
Vomiting	Has been grade 1 or 0 for the previous cycle or grade 2 for a maximum of 2 days
Nausea	Any grade in previous cycles acceptable
Peripheral neuropathy	Any grade in previous cycles acceptable
Temperature	All temperatures below 37.5

The primary outcomes defined were toxicities and achieved dose intensity as a percentage of standard dose intensity for this chemotherapy regimen. Secondary outcomes included summaries of advice generated by the system, number of amber and red alerts, management of toxicity against the guidelines, and patient and staff experience.

STATA version 11 was used for the quantitative and descriptive analysis, though some summaries were obtained directly from the software analysing the data transmitted by the phone. Frequency tables were used to demonstrate how often patients received each piece of advice from the system

Table 3 Dose reduction parameters

Parameter	Action
WBC count grade 4	Delay treatment then reduce capecitabine by 15 % and reduce oxaliplatin/docetaxel
WBC count grade 3	Delay treatment then restart capecitabine at the previous dose and reduce oxaliplatin/docetaxel
WBC count grade 2	Delay treatment then restart all agents at the previous dose
WBC count grade 1	Treat on time at the previous dose and consider capecitabine dose escalation
Neutrophils>1.5 and platelets>100	Consider for capecitabine dose escalation
Creatinine clearance 30–50 ml/min (moderate impairment; calculated according to Cockcroft–Gault formula)	Reduce capecitabine by 30 %
Creatinine clearance≤30 ml/min	Stop capecitabine

including recommendations on dose and on self-treating side effects.

Results

Although the trial was run in two phases, no major changes were made to the algorithm after phase I. Data are presented overall for all patients in phases I and II combined. Of the 39 patients assessed for eligibility, seven did not meet the eligibility criteria, six patients were eligible but declined, and the remaining 26 patients entered the trial (Fig. 3). Table 4 gives the baseline characteristics of these 26 patients.

In this trial, 26 patients received a total of 132 cycles of chemotherapy (median 5 cycles per patient). On 92.6 % occasions patients completed the diary (range 73.7–100 %). A summary of toxicity and dose escalations for two patients is shown in Fig. 4, and for all patients, see Online resource 1. Of the 26 patients entered in the study, three patients developed maximum CTCAE grade 1 toxicity, 11 patients maximum grade 2 and 12 patients maximum grade 3 toxicity. None of the patients developed grade 4 toxicity.

There were 11 occasions (ten patients) where patients experiencing a serious adverse event (SAE) were advised by the specialist nurses to be admitted to hospital: two patients due to diarrhoea and vomiting, two patients admitted for severe nausea, one patient with chest pain, one patient once with diarrhoea and once with hypokalaemia, one patient with abdominal pain, one patient with sepsis (non-neutropenic) secondary to a chest infection, one with neutropenic sepsis and one patient who then developed superior vena cava obstruction. None of these SAEs was assessed as related to the DATACAP study.

In summary (n=26), eight patients (31 %) required a dose reduction and eight patients (31 %) managed a dose increase, with five of these patients (19 %) reaching the 110 % dose level, two patients (8 %) reaching the 120 % dose level and one patient (4 %) achieving the 130 % dose level (Fig. 5). No patient who had to interrupt their cycle of therapy due to toxicity made a sufficient recovery during that cycle to restart taking the capecitabine within the same cycle.

Twelve patients had a maximum toxicity grade of at least 3 (46.2 % of patients), and the average dose intensity as a percentage of standard dose was 90 %. Eighteen patients (69 %) achieved at least an 80 % dose intensity as a percentage of standard dose.

As a sensitivity analysis, these summaries of toxicity and dose intensity were recalculated for the 40/132 (30 %) cycles in 14 patients with complete information. Within these, seven patients had a maximum toxicity grade of at least 3 (50 %), and the average dose intensity as a percentage of standard dose was 90 %, which are similar estimates to those calculated for all patients.

Secondary endpoints

On 396 occasions, self-care advice messages were sent to the patients as detailed in Table 5. Self-care messages were not sent for mucositis/peripheral neuropathy red/amber alerts and

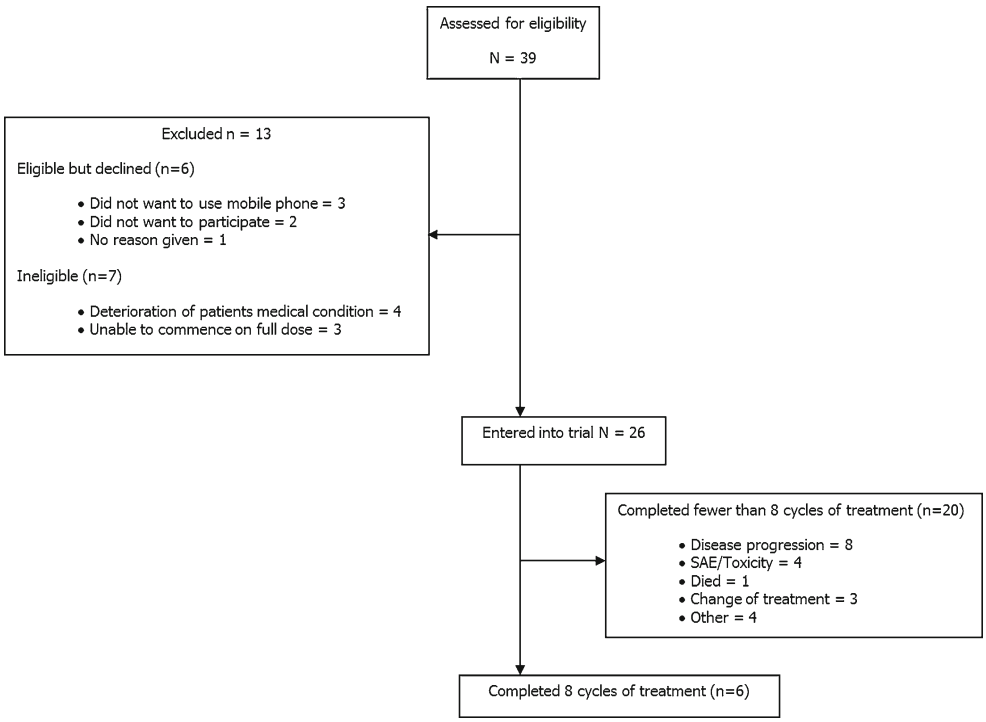

Fig. 3 Eligibility assessment

Table 4 Baseline characteristics

Cancer site	Breast	Colorectal		All patients
	Capecitabine 2,000 mg/m^2/week	Capecitabine 2,000 mg/m^2/week + Oxaliplatin	Capecitabine 2,500 mg/m^2/week	
Total recruited (%)	8 (31)	17 (65)	1 (4)	26 (100)
Age at recruitment				
Mean	53	58	66	57
Median (range)	56 (37–66)	62 (31–72)	–	60 (31–72)
Sex				
Male (%)	0	13	1	14 (53.8)
Female	8	4	0	12
Body surface area (*square meter*)				
Mean	1.81	2.03	1.99	1.96
Median (range)	1.78 (1.61–2.17)	2.11 (1.42–2.48)	–	1.93 (1.42–2.48)

messages to stop taking capecitabine were not sent for red alerts occurring when the patient was not taking capecitabine.

A summary of the alerts generated are shown in Table 6. The genuine alerts include alerts triggered from patients with toxicity/temperature readings that warrant attention. Other alerts include alerts triggered for example because of transmission problems or incorrect data entered by the patient. If the application could not upload the data due to reception

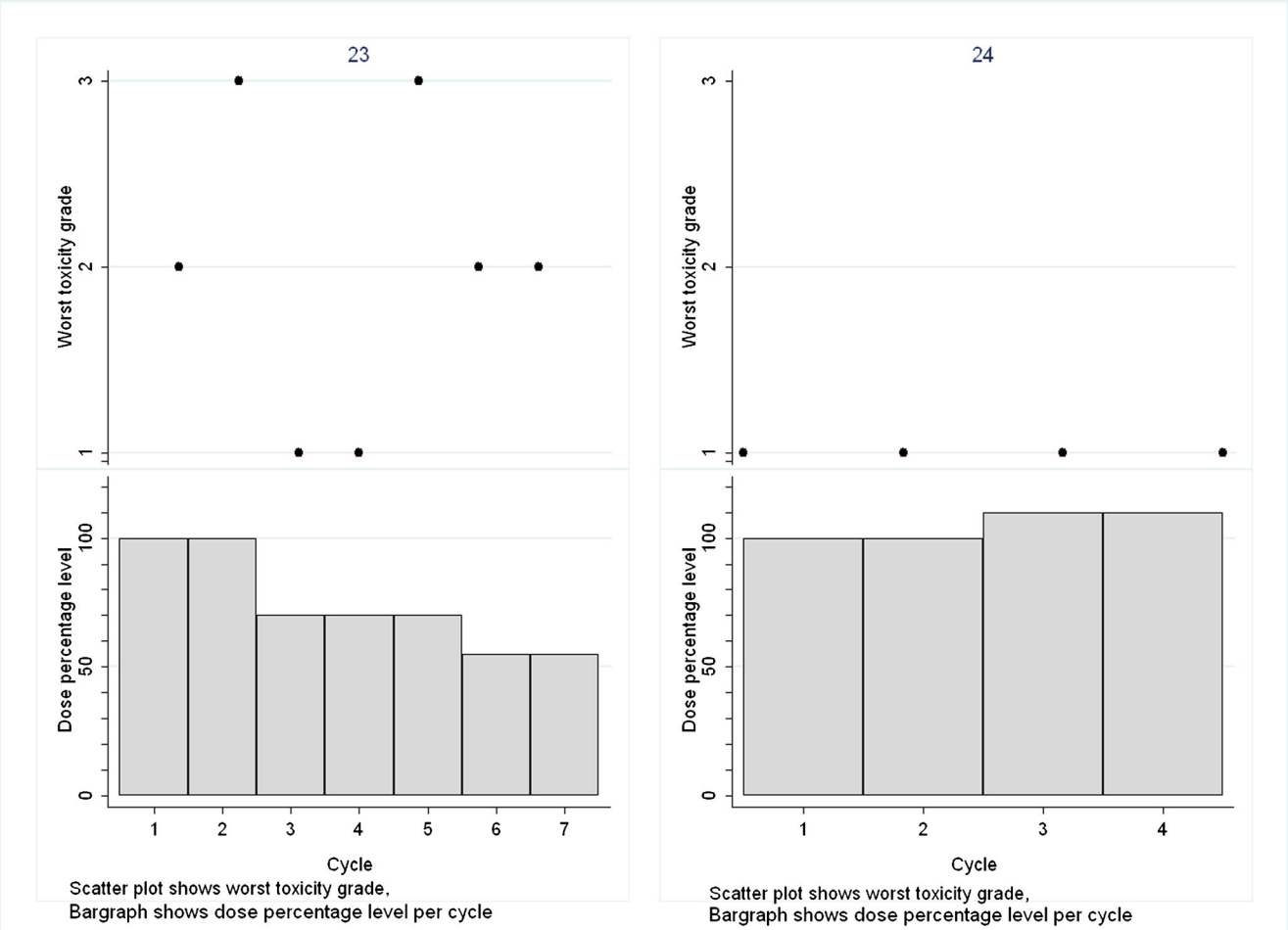

Fig. 4 Summary of worst toxicity grade and dose percentages per cycle for two patients. Scatter plots show worst toxicity grade and bar-graph shows dose percentage level per cycle

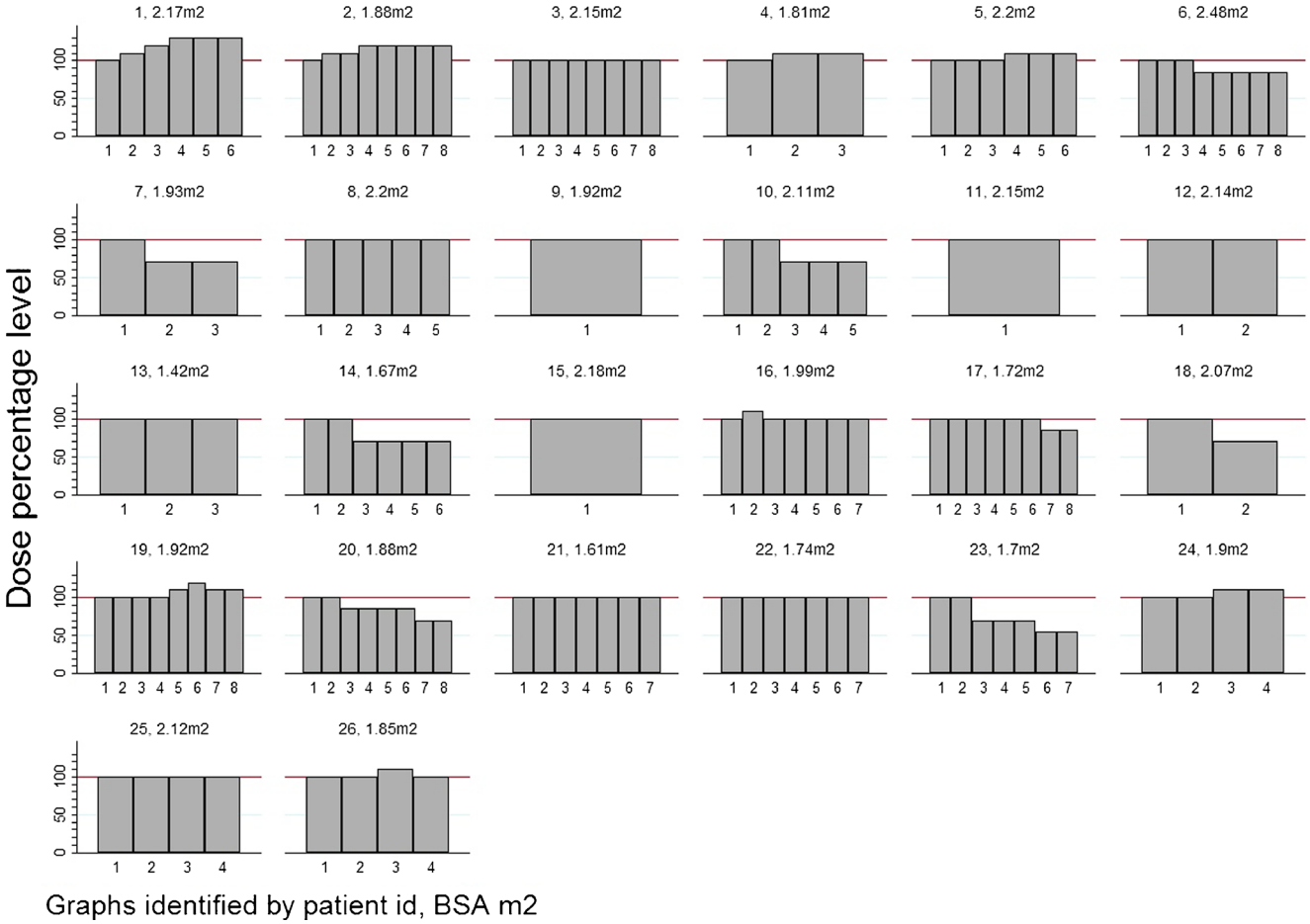

Fig. 5 Summary of dose percentages per cycle for all patients (n=26)

problems, the data were saved on the handset and automatically uploaded the next time the application was used. For one patient, the SIM card was swapped to one from an alternative network provider with better reception at their home, and one

Table 5 Frequency of advice messages provided by the phone

Alert type	Symptom/toxicity	Self-care message	Total (percent)
Amber	Diarrhoea	Take your loperamide capsules as prescribed. Drink plenty of fluids.	42 (10.6)
	Nausea/vomiting	Take your anti-sickness medication as directed.	66 (16.7)
	Hand–foot syndrome	Use your moisturizer as directed.	132 (33.3)
	Diarrhoea + nausea/vomiting	Take your loperamide capsules as prescribed. Drink plenty of fluids. Take your antisickness medication as directed.	3 (0.8)
	Diarrhoea + hand–foot syndrome	Take your loperamide capsules as prescribed. Drink plenty of fluids. Use your moisturiser as directed.	1 (0.3)
	Nausea/vomiting + hand–foot syndrome	Use your moisturiser as directed. Take your anti-sickness medication as directed.	8 (2.0)
Red*	Diarrhoea, vomiting, mucositis, temperature or hand–foot syndrome	Stop taking your capecitabine tablets. Do not start taking your capecitabine tablets again until you are advised to do so by the nurse.	144 (36.4)
Total			396

* In addition, self-care advice messages would be shown for each symptom

Table 6 Number of system generated alerts

Type of alerts		Red (percent)	Amber (percent)
Genuine alerts	Toxicity	38 (7.1)	449 (31.6)
	Temperature readings	11 (2.1)	8 (0.6)
	Compliance (failure to submit readings in time window)		
	Readings submitted late morning	21 (3.9)	350 (24.6)
	Compliance (reason known, e.g. patient in hospital)	262 (49.2)	57 (4.0)
	Compliance (reason unknown, e.g. patient did not fill in diary)	76 (14.3)	263 (18.5)
Other alerts	Patient data entry error (dose and toxicity)	47 (8.8)	5 (0.4)
	Transmission (diaries completed but not transmitted)	48 (9.0)	265 (18.6)
	Technical	24 (4.5)	11 (0.8)
	Duplicated alerts	3 (0.6)	8 (0.6)
	Server	1 (0.2)	4 (0.3)
	Network problem	1 (0.2)	2 (0.1)
Total		532	1,422

patient withdrew due to poor reception on all networks. There were 1,954 generated alerts during the study: 532 red and 1,422 amber. Of these 1,954 alerts, 487/1954 (24.9 %) were genuine toxicity alerts: 38/532 (7.1 %) red and 449/1422 (31.6 %) amber. Of the 38 red alerts for toxicity, 13/38 (34.2 %) occurred when the patient was not taking capecitabine and continued to submit readings.

There was a median of 103 (12–183) alerts per patient. All toxicity management was undertaken according to the guidelines according to an agreed protocol, now called the UKONS Triage Tool [8].

Twelve patients (46 %) were able to provide comments on the system and subsequent care. Real-time monitoring contributed to most patients 'feeling safe'. Patients also commented that the prompt response from the nurse whenever they had a medical or technical problem was reassuring. Patients stated that they closely followed the self-care advice. This advice from the phone application generally improved patients' confidence in their ability to self-manage and some patients reported being 'in control' of their care. Interestingly, one patient suffering from anticipatory nausea struggled with entering data as this exacerbated her symptoms. Conversely, another patient found it easier to report symptoms of diarrhoea on the phone rather than face-to-face which he found embarrassing.

The study nurses (n=5) noted that they felt in touch with their patients, confident their patients' side effects were being managed promptly. The nurses had more day-to-day contact with their patients as a result of the study. Initially, ward nursing staff found the effort of responding to out of hour alerts demanding in an already busy environment. However, over time and through increasing experience and confidence, they perceived DATACAP as an excellent system for an out of hours service.

The nurses reported that the study website displaying individual patient reports was a first-rate resource and tool for the clinical team at patient's end-of-cycle review. They commented that the side effects occurring early in the cycle which patients often failed to recall were clear on the report, thereby creating an accurate real-time picture of the patient's symptoms during the entire cycle.

Discussion

In one of the first studies of its kind in cancer patients, we have demonstrated that using a mobile phone application, it is possible to safely monitor chemotherapy toxicity in real time, thereby promoting appropriate dose adaptations. During usual care, the clinician often has to make a decision on dose adjustments between cycles of chemotherapy according to the patient's recollection of side effects and honesty of reporting at the clinic visit. The continuous real-time data enabled dose increases and provided instant access to an individual patient's toxicity profile. Likewise, dose reductions/interruptions in real time, compared to between-cycle changes, resulted in proactive management of the patient. Dose reduction increments were lower than standard protocols, providing the opportunity for a more dose-intense regimen. Symptoms were also managed in real time with prompting for self-care action via the phone application and in more severe cases via a phone call from a nurse. These factors, we believe, are more efficient means of toxicity monitoring, compared with relying on the patient to ring into hospital to report their side effects or assessing toxicity only at the clinic visit. This is also one of the few published studies showing that it is possible to dose escalate capecitabine beyond the standard dose.

We have demonstrated an average dose intensity level of 90 % of the planned dose intensity. This is similar to the 12-week dose intensity for capecitabine in the COIN [9] trial at 88 % (comparable patients with metastatic disease), the X-ACT trial [10] in which patients receiving adjuvant capecitabine achieved 89 % dose intensity, and the recent study of adjuvant capecitabine in elderly patients with colon cancer in which 50 % of patients maintained relative dose intensity of >80 % with both dose escalations and reduction [11].

Close scrutiny of the red alerts revealed that the majority of these were related to diaries not being completed within the required time interval. The number of alerts could be significantly reduced by a small change in the software to allow time intervals between data entry tailored to the patient's lifestyle.

The red and amber alerts were a valuable warning system of progressive toxicity with the amber alerts offering advice on the phone for the patients to self-manage. As expected, red alerts were also received when the patients were not taking capecitabine tablets during their treatment cycle. Study funding allowed for a short interview to investigate patient and staff experience. A limitation of the study is the lack of an in-depth qualitative patient experience substudy which may aid more rapid transferability into large-scale practice.

Early intervention for management of toxicity was evident. This integrates well with the principles of 'acute oncology', formalised in the UK in 2009 [12], and provides an efficient system for monitoring toxicity arising from chemotherapy, radiotherapy and acute cancer-related complications, when used in conjunction with international triage criteria [8]. This is our proposed UK telehealthcare model of the future, currently under service evaluation.

Overall, we have demonstrated that adaptation of individual capecitabine dose is possible using mobile phone technology, thereby maintaining maximum dose intensity whilst minimising toxicity. Specialist oncology staff are able to safely follow and rapidly manage moderate and severe toxicities in real time. Patients receiving chemotherapy are able to use a mobile phone application with ease and self-manage mild toxicity. The next phase of development is to conduct a randomised controlled trial comparing the toxicity and dose intensity effect of the phone-based toxicity monitoring with usual care.

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Conflict of interest LT was a co-founder of t+ Medical, the company which hosted the study server. All remaining authors have declared no conflict of interest.

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