Supportive Care in Cancer (2019) 27:2189–2194
https://doi.org/10.1007/s00520-018-4505-6

ORIGINAL ARTICLE

Prospective study of a web-mediated management of febrile neutropenia related to chemotherapy (Bioconnect)

Fabrice Denis[1,2] · Eric Voog[1] · Yoann Pointreau[1] · Hugues Bourgeois[1] · Valérie Seegers[3] · Katell Le Du[1]

Received: 13 June 2017 / Accepted: 5 October 2018 / Published online: 10 October 2018

Abstract

Background We aimed to investigate whether patient self-evaluated symptoms transmitted via Internet is feasible between planned visits to provide an early management of fever and neutropenia induced by chemotherapy, and if it can reduce hospitalizations for severe neutropenia.

Methods Patients who received a chemotherapy regimen with an overall risk of febrile neutropenia ≥ 20% had to report daily temperature between physician planned visits using a web application. Fever and clinical signs of seriousness were reported to the physician (if some criteria were fulfilled in a specific algorithm) via automatic email notifications by the web application. Patients could be hospitalized quickly or could take over at home, make blood count, and take predefined oral antibiotics if indicated. Primary outcome was patient's compliance and satisfaction. The number and the cost of hospitalization were also assessed and compared with an historical cohort of patients with similar clinical conditions and treatment.

Results Among the 41 patients included, 36 (87.8%) used the web application with 88% of daily compliance and 90% (28/33) of satisfaction. One patient (2.7%) had planned hospitalization after the web application alert. In the historical cohort, the rate of unplanned hospitalization for febrile neutropenia was 17% (6 patients) and 2.7% (1 patient) in users of the web application cohort. The cumulative cost of hospitalization for neutropenia was USD 28,827 in the historical cohort and USD 6563 in the web application cohort.

Conclusion Web-mediated follow-up of febrile neutropenia is feasible. It led to high patient satisfaction, high compliance, and a possible reduction of the number and the cost of hospitalizations.

Keywords e-health · Neutropenia · Chemotherapy · Clinical trial

Introduction

Patient self-reported outcomes in oncology recently received a growing interest for their potential to improve the follow-up of symptoms and the efficiency of clinical care [1, 2]. The health-related qualify of life was thus improved in patients whose symptoms were monitored during routine cancer care [3, 4]. Recent prospective randomized studies also suggested survival improvement in cancer patients using web-mediated follow-up called Moovcare™ which allowed early detection of relapses and dangerous medical conditions [5–8].

Febrile neutropenia is defined as fever superior or equal to 38.3 °C and an absolute neutrophil count inferior to 1000/mm^3. It is a frequent and potentially severe complication of chemotherapy [9]. It requires rapid management using antimicrobial agents according to guidelines [10]. Patients are usually informed by the physician that febrile neutropenia is possible and that they should call him if fever occurs. However, communication of symptoms and the assessment of severity are not optimal. Although primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) reduces febrile neutropenia incidence by 46% in a meta-analysis, this event leads to unplanned and expensive hospitalizations and lethal complications subsequently to the delay in fever management in some patients [9, 11–13].

✉ Fabrice Denis
f.denis@cjb72.org

[1] Institut Inter-régional de Cancérologie Jean Bernard, 9 rue Beauverger, Le Mans, France

[2] CORIA UMR 6614—Normandie Université, CNRS – Université et INSA de Rouen, Campus Universitaire du Madrillet, F-76800 Saint-Étienne-du-Rouvray, France

[3] Institut de Cancérologie de l'Ouest Paul Papin, 15 rue A Boquel, 49100 Angers, France

Web-mediated follow-up may optimize communication of symptoms and blood results between patients and physicians and is able to tailor and accelerate the process of febrile neutropenia management in patients under high-risk chemotherapy. We report the results of a prospective trial designed to assess the feasibility of a follow-up by a web application. The compliance and the satisfaction of patients using a web application with a specific algorithm triggering email notifications to physicians, as well as the number and the cost of hospitalization related to febrile neutropenia management were assessed.

Materials and methods

Study design and population

In this study, eligible patients had histologically proven solid or hematological tumors regardless of the location (except brain tumor) and should receive chemotherapy (any indications) associated with overall risk of febrile neutropenia greater than or equal to 20%. Overall risk was defined using NCCN guidelines and took into account chemotherapy regimen and patient risk factors such as age 65 and older, previous chemotherapy or radiotherapy, poor performance status, or poor renal or liver function [14]. Patients with brain metastasis or dementia were excluded. Chemotherapy duration must be inferior to 4 months, that is, four to six cycles. Performance status was 0 to 3 and patients must have had Internet familiarity and prior email experience. Prophylactic G-CSF was allowed and provided to all patients as well as for treatment of febrile neutropenia if needed. All patients provided their written informed consent. The study was conducted by the Integrated Center for Oncology (ICO, Angers, France) which gathered the data using an electronic case report form (e-CRF).

Web-mediated follow-up

We designed a web application allowing patients to send daily their temperature and self-evaluate symptoms to the physician between planned visits via Internet using a smartphone or a personal computer. Five days after the day 0 of the first cycle of chemotherapy administration, the use of the application was initiated and temperature measurement was performed at home by an infrared forehead thermometer provided as part of the study, in a systematic manner once daily at the same time of day and in case of unexplained fatigue. An online form was also completed by the patient looking for clinical signs of seriousness to assess condition if fever was superior or equal to 38.3 °C. Clinical signs of seriousness were as follows: fever superior to 39.5 °C, the presence of shivers, a brutal asthenia, a decrease in urine volume, an important breathlessness, pain when swallowing, or blood in mouth. If some criteria were fulfilled in a specific algorithm, automatic email notifications were triggered to the physician by the web application. For example, if one clinical sign of seriousness was reported by the patient, a notification was sent to medical team which called the patient by phone. The patient could then have quick planned hospitalization (that is, without a consultation or a passage at the emergency unit). Without seriousness, the patient could stay at home and the application requested him to make blood count, then to send results of neutrophil count using application and to take predefined oral antibiotics if neutrophil count was inferior to 1000/mm^3. New notification to medical team occurred if new clinical signs of seriousness occurred or if fever was reported despite 2 days with antibiotics. Planned hospitalization could then be decided by the physician. The physician performed an initial 5-min demonstration of the use of software after enrollment and an email with instructions and password was then sent to patients. The prototype of the application used in this study had no automatic reminder to uncompliant patient Fig. 1.

Outcome assessment

The first primary outcome was patient compliance rate. The longitudinal compliance rate was computed as the ratio between the number of forms filled in by the participants and the theoretical maximal number of forms that the patients included should have filled in between the fifth day of the first cycle of chemotherapy and 3 weeks after the last chemotherapy. The second was the opinion of the patients regarding this

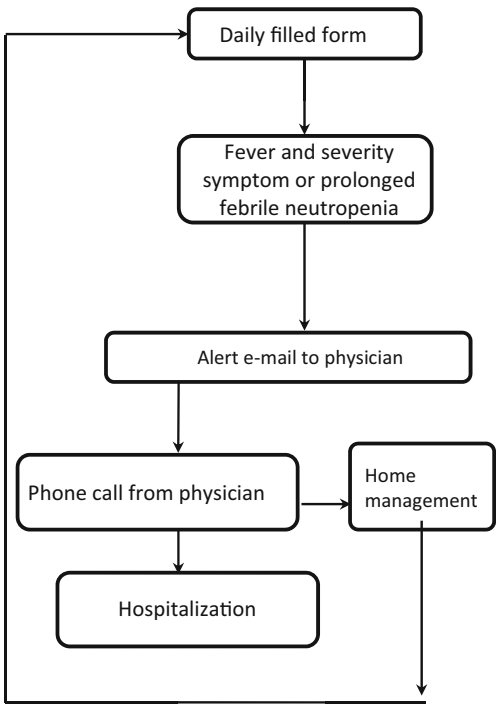

Fig. 1 Decisional tree in the web-mediated follow-up cohort

application which was assessed through a satisfaction survey completed just after the last cycle of chemotherapy. The questions were:

a. "Do you feel reassured when monitored by your oncologist using the Bioconnect follow-up?"
b. "Do you feel anxious when you fill in the form each day?"
c. "Do you consider the Bioconnect web application easy to use?"
d. "Do you feel better monitored by your oncologist with this application?"
e. "Are you generally satisfied with this application?" The secondary endpoints were the number and cost of unplanned emergency hospitalizations for febrile neutropenia.

Patients were followed from the fifth day after the day 0 of the first chemotherapy cycle to the end of the last cycle, that is, 3 weeks after the final cycle of chemotherapy.

An analysis of the primary endpoints was computed after 41 patients' enrollment in intent-to-treat (ITT) analysis and in a per-protocol analysis. Patients who did never use the application before a first event were kept in ITT analysis and removed from per-protocol analysis (5 patients).

Accuracy rates of this exploratory analysis were determined according to our previous feasibility results [5–7]. To deserve further development, the satisfaction and the longitudinal compliance had to be greater than 75% (lower bound of CI 95 equal to 60%).

In experimental cohort, patients were hospitalized if clinical signs of seriousness were reported by a patient during a phone call from the physician who received blood count which showed neutropenia or if fever was reported by a patient despite 2 days of antibiotics.

A comparison of the rate and cost of unplanned emergency hospitalizations in the experimental cohort was made with an historical cohort of 36 consecutive patients who were treated in the same center and followed between May 2015 and September 2015, that is, just before the initiation of the study. Costs of hospitalization were directly reported from the electronic medical record of the medical centers. It contained daily cost of stays and delivered treatments.

Patients must have had similar clinical conditions and they all had G-CSF prophylaxis and treatments. No significant changes between chemotherapy regimens occurred between the two periods and between the two cohorts. This study was registered in ClinicalTrials.gov (NCT02866851).

Descriptive analyses were computed using R version 3.3.2 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/)

Results

Patients characteristics

Between September 2015 and August 2016, 41 patients were enrolled in this prospective study. No patient explicitly canceled his participation to the study. Five patients were deemed ineligible after inclusion in per-protocol analysis because they did not use application subsequently to a lack of Internet connection or a wish not to use it. They had routine monitoring. Patients who had at least one connection to the application before any event were assessable for user (per-protocol) analysis.

Patient characteristics of the patients in ITT and per-protocol analyses are reported in Table 1.

Primary outcomes

Daily longitudinal compliance rate of web application use was 81.2% (interquartile range = 46.2–100%, μ = 67.2%, σ = 35.8) for the intent-to-treat patient's cohort and 88.4% (interquartile range = 53.2–100%, μ = 76.5%, σ = 27) in user cohort (per-protocol analysis). Satisfaction of patients was observed in 90.3% of the 31 patients who filled out the form (Table 2). They considered the application easy to use (83.9%), and felt better monitored by their oncologist (80.6%). Ten users did not fill out the satisfaction form: 5 patients did never connect, 1 was lost of follow-up after chemotherapy, 3 had cancer complications and wished not to fill it out, and 1 forgot it despite 3 recall.

Secondary outcomes

In intent-to-treat population (41 patients), 2 patients had grade 4 febrile neutropenia and required hospitalization.

One (2.7%) had a planned hospitalization, that is, an hospitalization preceded by a notification of the application to the physician who contacted the patient by phone and organized an hospitalization in a medical service without going in an emergency room. This hospitalization costed USD 3328 and lasted 4 days.

The second one (2.7%) had a non-planned emergency hospitalization which costed USD 3235 and lasted 1 day. Therefore, the cumulative cost of these hospitalizations was USD 6563 with a mean cost per patient for this cohort of USD 182.

Two other patients had fever without neutropenia

In the historical cohort with routine follow-up, the rate of unplanned emergency hospitalizations for febrile neutropenia was 17% (6 patients, one episode per patient), and the mean

Table 1 Baseline characteristics of intent-to-treat, per-protocol (users of the web application), and historical cohorts

	Intent-to-treat population $N = 41$ (%)	Per-protocol population $N = 36$ (%)	Historical cohort $N = 36$ (%)	P*
Age				
Median (min-max)	59 (21–88)	60 (44–85)	61 (29–84)	NS/NS
Sex				
Men	16 (39.0)	13 (36.1)	17 (47.2)	NS/NS
Women	25 (61.0)	23 (63.9)	19 (52.8)	
Performance status				
PS 0	19 (46.3)	15 (41.7)	16 (44.4)	NS/NS
PS 1	19 (46.3)	19 (52.8)	17 (47.2)	
PS 2	3 (7.3)	2 (5.5)	3 (8.3)	
Primary tumor				
Lung	5 (12.2)	4 (11.1)	4 (11.1)	NS/NS
Pancreas	1 (2.4)	1 (2.8)	1 (2.8)	
Non-Hodgkin lymphoma	15 (36.6)	15 (41.7)	15 (41.7)	
Hodgkin lymphoma	4 (9.8)	3 (8.3)	3 (8.3)	
Head and neck	2 (4.9)	1 (2.8)	1 (2.8)	
Breast	13 (31.7)	11 (30.6)	11 (30.6)	
Bladder	1 (2.4)	1 (2.8)	1 (2.8)	
Treatment received				NS/NS
(R)CHOP	12 (29.3)	12 (33.3)	14 (38.9)	
Docetaxel-cyclophosphamide	5 (12.2)	5 (13.9)	5 (13.9)	
Doxorubicine-cyclophosphamide	7 (17.1)	6 (16.7)	6 (16.7)	
BEACOPP	2 (4.9)	1 (2.8)	2 (5.5)	
ABVD ± R	2 (4.9)	2 (5.5)	1 (2.8)	
TPF	2 (4.9)	1 (2.8)	1 (2.8)	
FOLFIRINOX	1 (2.4)	1 (2.8)	1 (2.8)	
MVAC	1 (2.4)	1 (2.8)	1 (2.8)	
R-DHA oxaliplatin	1 (2.4)	1 (2.8)	1 (2.8)	
R-ICE/RFC	2 (4.9)	2 (5.5)	0	
Carboplatin—experimental therapy	1 (2.4)	0	0	
Carboplatin-(Nab) paclitaxel + (Herceptin or bevacizumab or experimental therapy)	5 (12.2)	4 (11.1)	4 (11.1)	

*The P value is obtained from the two-sided chi-square or Fisher test. First value compares intent-to-treat cohort to historical cohort and second value compares per-protocol cohort to historical cohort

R-CHOP = rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone,

R-ICE = rituximab + etoposide + carboplatin + ifosphamide,

RFC = rituximab + fludarabine + cyclophosphamide,

BVD = doxorubicin + vinblastine + bleomycin + dacarbazine,

BEACOPP = doxorubicin + vincristine + cyclophosphamide + bleomycin + etoposide,

R-DHA oxaliplatin = rituximab + cytarabine + oxaliplatin + dexamethasone,

TPF = docetaxel + cisplatyl + 5-fluoro uracyl,

FOLFIRINOX = 5-fluoro uracyl + irinotecan + oxaliplatin,

MVAC = methotrexate + cisplatyl + vinblastine + doxorubicin

duration of these hospitalizations was 9 days (min 3 days, max 15 days). The cumulative cost of these hospitalizations was USD 28,827 with a mean cost per patient for this historical cohort of USD 800.

Discussion

This prospective trial is the first which assessed the feasibility of a web-mediated follow-up of cancer patients undergoing

Table 2 Opinion of the patients who used the application (assessed in 31 patients). 95% confidence intervals are just calculated for high values of %

	Yes *n* (%) -[CI 95]	No *n* (%) -[CI 95]	No opinion *n* (%) -[CI 95]
Do you feel reassured when monitored by your oncologist using the Bioconnect follow-up?	27 *(87.1%) -[75.3–98.9]*	3 (9.7%)	1 (3.2%)
Do you feel anxious when you fill in the form each day?	2 (6.5%)	28 *(90.3%) -[79.9–100]*	1 (3.2%)
Do you consider the Bioconnect web application easy to use?	26 *(83.9%) -[71.0–96.8]*	4 (12.9%)	1 (3.2%)
Do you feel better monitored by your oncologist with this application?	25 *(80.6%) -[66.7–94.5]*	5 (16.1%)	1 (3.2%)
Are you generally satisfied with this application?	28 *(90.3%) -[79.9–100]*	1 (3.2%)	2 (6.5%)

chemotherapy having high risk of febrile neutropenia. It showed satisfaction in almost all users and a high longitudinal compliance rate. One (2.7%) unplanned hospitalization was observed in users, although 17% were reported in an historical cohort of patients having similar disease and characteristics.

Web-mediated follow-up was already assessed in prospective trials and showed benefit in quality of life and in survival, as well as cost-effectiveness [2, 3, 7, 8].

We already showed a high level of satisfaction (100%) and compliance (84%) with another web application for relapse detection of lung cancer and kept the same friendly interface for Bioconnect web application prototype [7]. This may explain the high compliance level in this study, although the daily connection could have reduced patient adherence compared to a weekly connection in lung cancer trial.

The low cost of hospitalization for severe hematological conditions in our trial may be subsequent to an earlier management of fever allowed by the web application which sent notifications in real time to both physician and patient in order to manage him at the first symptoms of febrile neutropenia. This may lead to reduce the cost and the duration of hospitalizations and potentially severe sepsis complications. As recently reported, the clinical burden induced by chemotherapy-induced febrile neutropenia is still considerable. In France, using the National Health Insurance (PMSI) database, which includes all hospitalizations occurring annually, the rate of hospitalization for febrile neutropenia in newly diagnosed patients was of 7.4% in 2010–2011, with a mortality rate of 7%. In the USA, the total cost of cancer-related neutropenia hospitalizations was $2.3 billion for adults and $439 million for children. Cancer-related neutropenia hospitalizations accounted for 5.2% of all cancer-related hospitalizations and 8.3% of all cancer-related hospitalization costs. For adults, the mean length of stay for cancer-related neutropenia hospitalizations was 9.6 days, with a mean hospital cost of $24,770 per stay. For children, the mean length of stay for cancer-related neutropenia hospitalizations was 8.5 days, with a mean hospital cost of $26,000 per stay [13]. We found the same mean length of stay in hospital in our historical cohort (9 days) and a shorter in experimental arm (1 and 4 days), suggesting a potential benefit of our approach on hospitalization duration.

We observed a low rate of FN in study cohort. Unfortunately, we cannot know if duration of G-CSF prophylaxis was different between historical and study cohorts. The difference of FN rate might be subsequent to the heterogeneity of population on other parameters than those selected for population characteristics description.

As this study is exploratory, interpretation has limitations subsequently to the low number of patients, and the comparison with an historical cohort of patients. However, it provides a rationale for the development of a larger multicentric trial. We are working on two large international studies in which Bioconnect will be integrated with other patient-reported outcome modules (such as Moovcare ™) to follow patients during all the cancer management pathway including treatment phase (chemotherapy, immunotherapy, targeted therapy) and to detect relapse and other clinical events. One will be randomized and will focus on quality of life and cost-effectiveness for good prognosis cancers, and the other will focus on survival and cost-effectiveness and will not be randomized. In both trials, the cost of hospitalization for FN will be exhaustively reported for several countries. This approach is a starting point for incorporating new technology into the management of patients with chemotherapy with which they can give and receive continuous feedback between visits to their physician.

Acknowledgements We thank the patients and their families for their participation in this study, as well as investigators, promotor: Integrated Center for Oncology (ICO, Angers, France), Anne-Lise Septans for statistical analysis, Magali Balavoine for trial monitoring, and sponsors: CHUGAI PHARMA France and SIVAN Innovation Ltd. for financial sponsorship.

Fundings This work was supported by CHUGAI PHARMA France and SIVAN Innovation Ltd.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Selby JV, Beal AC, Frank L (2012) The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. JAMA 307:1583–1584
2. Basch E, Artz D, Dulko D, Scher K, Sabbatini P, Hensley M, Mitra N, Speakman J, McCabe M, Schrag D (2005) Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol 23:3552–3561
3. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, Dionne-Odom JN, Frost J, Dragnev KH, Hegel MT, Azuero A, Ahles TA (2015) Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol 33:1438–1445
4. Basch E, Deal AM, Kris MG et al (2015) Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol 34:557–565
5. Denis F, Viger L, Charron A, Voog E, Letellier C (2014) Detecting lung cancer relapse using self-evaluation forms weekly filled at home: the sentinel follow-up. Support Care Cancer 22:79–85
6. Denis F, Viger L, Charron A, Voog E, Dupuis O, Pointreau Y, Letellier C (2014) Detection of lung cancer relapse using self-reported symptoms transmitted via an Internet web-application: pilot study of the sentinel follow-up. Support Care Cancer 22:1467–1473
7. Denis F, Yossi S, Septans AL et al (2015) Improving survival in patient treated for a lung cancer using self-evaluated symptoms reported via a web-application. Am J Clin Oncol
8. Denis F, Lethrosne C, Pourel N, Molinier O, Pointreau Y, Domont J, Bourgeois H, Senellart H, Trémolières P, Lizée T, Bennouna J, Urban T, el Khouri C, Charron A, Septans AL, Balavoine M, Landry S, Solal-Céligny P, Letellier C (2017) Randomized trial comparing a web-mediated follow-up to routine surveillance in lung cancer patients. J Natl Cancer Inst 109(9). https://doi.org/10.1093/jnci/djx029
9. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH (2006) Mortality, morbidity and cost associated with febrile neutropenia in adult cancer patients. Cancer 106(10):2258–2266
10. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 52(4):e56–e93
11. Kuderer NM, Dale DC, Crawford J, Lyman GH (2007) Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 25(21):3158–3167
12. Freyer G, Scotte F, Borget I, Bruyas A, Vainchtock A, Chouaid C (2016) Hospitalisations pour neutropénie fébrile chimio-induite en France en 2010–2011: impact clinique et caractéristiques des patients à partir des données de la base PMSI. Bull Cancer 103:552–560
13. Tai E, Guy GP, Dunbar A, Richardson LC (2017) Cost of cancer-related neutropenia or fever hospitalizations, United States, 2012. J Oncol Pract. https://doi.org/10.1200/JOP.2016.019588
14. (2012) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloid growth factors. v1