

Clinical Effects of Assessing Electronic Patient-Reported Outcomes Monitoring Symptomatic Toxicities During Breast Cancer Therapy – A Nationwide and Population-Based Study

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Short report

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Abstract

The involvement of cancer patients in symptom reporting talks into our cultural narrative of empowerment and participation in decisions in health of both patients and professionals. Electronic Patient Reported Outcomes (ePRO) is a tool applied for use in such interaction. Based on limited evidence and few empirical studies, health systems are rapidly implementing this instrument in managing patients in active treatment and in follow-up. In a cluster randomized trial of all Danish oncology departments treating breast cancer with adjuvant chemotherapy, we applied ePRO in 347 patients consecutively recruited. Our primary outcome, which was at least one treatment adjustment, was not significantly influenced using ePRO, 34% in the ePRO arm and 41% in the usual care arm received at least one treatment adjustment, $p=0,095$. Number of hospitalizations and events of febrile neutropenia was not influenced by the intervention. We believe that one of the main reasons for this finding could be the application of PRO in a well-regulated treatment setting within a public health care system where the most impacting symptomatic toxicities are already taken care off.

ClinicalTrials.gov Identifier: NCT02996201, registered 19 December 2016, retrospectively registered.

Short Report

Information concerning symptomatic toxicities leading to treatment adjustments are currently being investigated applying a range of Patient Reported Outcome (PRO) instruments. The introduction of such measures acknowledges the discrepancy between symptoms reported by patients and clinicians (1–3). Promising results regarding symptom control (4, 5) and even survival (6, 7) have highlighted the potential clinical benefits based on regular registration of ePRO. However, studies published do have limitations by including highly selected, health-insured patients (6) or quite heterogeneous patients in terms of stage of disease at time of inclusion (7) reducing generalizability of the findings. Despite the preliminary and limited evidence, ePRO is currently being implemented across many health systems in different settings. Before publication of the landmark trials by Basch and Denis (6, 7) we planned, registered and initiated a nationwide, population-based randomized clinical trial examining the impact of applying ePRO in a public health system. We aimed at reducing treatment adjustments and hospitalizations, in breast cancer patients cluster-randomized immediately before initiating six cycles of standard adjuvant chemotherapy.

All 11 Danish departments treating breast cancer patients with adjuvant chemotherapy (8) (9) took part in the study. Departments were randomized either to let the patients use an electronic PRO questionnaire with real-time feedback to clinicians (ePRO arm) for reporting of symptom toxicity during chemotherapy or to use standard methods for handling of symptomatic toxicities. Stratification for department size and geography was applied. The ePRO presented 42 PRO-CTCAE questions (10, 11) on 25 symptoms to the patients (12). At departments randomized to use ePRO (Fig. 1a), patients completed a questionnaire on a tablet computer before each cycle of chemotherapy and current and past reporting was presented to the clinicians (13). Reviewing of data was not mandatory for the health professionals.

Primary endpoint was number of patients with one or more treatment adjustment; secondary endpoints were number of patients with one or more hospitalizations and one or more events of febrile neutropenia. Number of patients with treatment postponed more than seven days as well as completion of the scheduled six cycles of chemotherapy were registered. Compliance to ePRO was measured by the number of answered questionnaires. The study had a power of 80% to detect a difference of 15 percentage points for ePRO arm versus usual care arm for the treatment adjustment, which has been reported to occur in approximately 50% of patients (40–62%) (14) and 5 percentage points (10 to 5%) for the secondary outcomes. For this purpose, 700 patients were needed. A generalized linear mixed model analysis was performed for each of the three binominal endpoints adjusting for age and treatment regimen using SAS 9.4

Of 682 patients enrolled, 347 (ePRO arm) and 335 (usual care arm) (Fig. 1b), the median age was 53 years in both arms (range 21–82). Baseline variables were well balanced, apart from treatment regimens. In total, 34% in the ePRO arm and 41% in the usual care arm received at least one treatment adjustment; however, this difference was not statistically significant (Fig. 2a). No difference was found regarding hospitalization or febrile neutropenia (Fig. 2a).

In the ePRO arm, 32% had at least one chemotherapy cycle postponed (≥ 7 days), compared to 38% in the usual care arm (Fig. 2b). The six scheduled cycles of chemotherapy were completed without treatment adjustments in 66% (ePRO arm) and 59% (usual care arm) (Fig. 2b).

Compliance in the ePRO arm was 87%, as patients answered 1,747 questionnaires out of 2,015 possible. 63% in the ePRO arm had the completions of the electronic PRO questionnaire reviewed by a health professional at least once.

Contrary to our expectations, we did not find a significant effect on our main outcomes. We carried out the study in a tax-paid, public health system, free of charge for every citizen implying that patients fragile due to existing comorbidity, social status and psychological functioning are a part of the population admitted to the oncology clinic. Despite the non-significant character of our findings, the overall results point in the direction of clinical value as previously reported in a population of metastatic cancer patients from the US (6) and a population of French lung cancer patients (7).

The fact, that only a non-significant effect of the intervention was observed may be influenced by two conditions. First, the intervention might be of low potency compared to usual practice if the most impacting symptomatic toxicities are already taken care off. This consideration arises due to the content of the high-quality treatment program for breast cancer patients following Danish national guidelines and the tax-paid public health system, www.DBCG.dk. Second, the study was underpowered to detect an existing difference between the study arms, as the frequency of dose adjustments (34–40%) in both study arms turned out to be less than anticipated (50%) when the study was planned. Number of hospitalizations was high in both study arms, however this excess number of hospital events was also reported in a large cohort study of more than 8,000 breast cancer women in Canada (15). Due to existing workload we were not able to include mandatory review of patients' PRO reporting, which is reflected in

the number of reviews. This is a weakness, since improved patient-clinician communication is needed for better management of symptomatic adverse events, and the study would have benefited from a more detailed analysis of this issue. Further, in our study report of severe symptoms did not automatically alerted the providers for further intervention. In this context the establishment of clinical guidelines, which outline mandatory review by health professionals of PRO information and guidance for intervention would possibly influence the effect of implementing PRO during treatment of a breast cancer patients.

To the best of our knowledge, we report the first randomized trial assessing a PRO instrument among cancer patients in active treatment following the two reports by Basch and Denis, respectively. We find no significant of using ePRO on our primary outcome and ascribe this result to several methodological issues within the study design and execution. The effect of implementation of ePRO in oncology may be highly dependent on the setting with respect to e.g. diagnosis, stage of disease, treatment type, population characteristics and health care system.

Declarations

Ethic approval and consent to participate

Ethics approval for the present study was not needed due to Danish law. The study was approved by the Danish Data Protection Agency (File number, 2015-41-4190) and registered at Clinicaltrials.gov (Clinicaltrials.gov identifier NCT02996201). All participants included completed informed consent.

Consent for publication

Not applicable

Availability of data and materials

The dataset used during the current study is available from the corresponding author on reasonable request.

Competing interest

The authors declare no competing interests in relation to the present publication.

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Authors contribution

HP, CWB, AaN and CJ designed the study and planned the implementation with AK. NHH designed the software. HP and CWB performed the study. CWB and JC performed the statistical analysis. All authors were actively involved in interpreting the results and writing the manuscript.

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List Of Abbreviations

PRO - Patient Reported Outcomes

ePRO - electronic Patient Reported Outcomes

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Figures

A



B

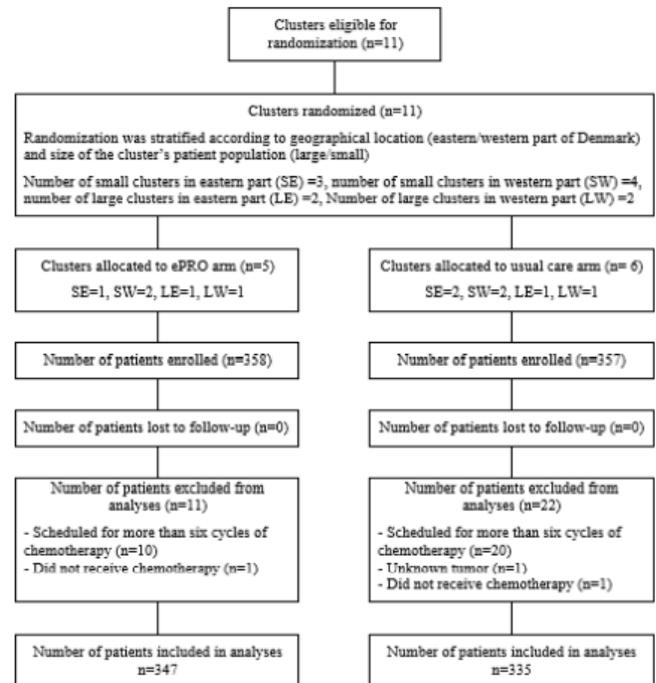


Figure 1

Randomization. A) Results of the cluster randomization stratified for geographic location and size of the cluster's patient population. B) CONSORT diagram of the randomization process.

A

	ePRO (n=347) n (%)	Usual care (n=335) n (%)	Odds Ratio (OR) for patients in the ePRO arm compared to the usual care arm ¹
Treatment adjustments²	118 (34.0)	136 (40.6)	OR=0.75, 95% CI:0.54-1.05, p=0.095 ³
Hospitalization	89 (25.6)	75 (22.4)	OR=0.90, 95% CI:0.60-1.35, p=0.616 ³
Febrile neutropenia	31 (8.9)	35 (10.4)	OR=0.72, 95% CI:0.40-1.28, p=0.257 ³

*Number of patients with minimum one event of febrile neutropenia/hospitalization/treatment adjustment during six cycles of chemotherapy
¹OR for having at least one event of treatment adjustment/hospitalization/febrile neutropenia
²Dose reduction or change of treatment regimen
³A generalized linear mixed model taking into account the cluster randomization was used. Models were adjusted for age and treatment regimen

B

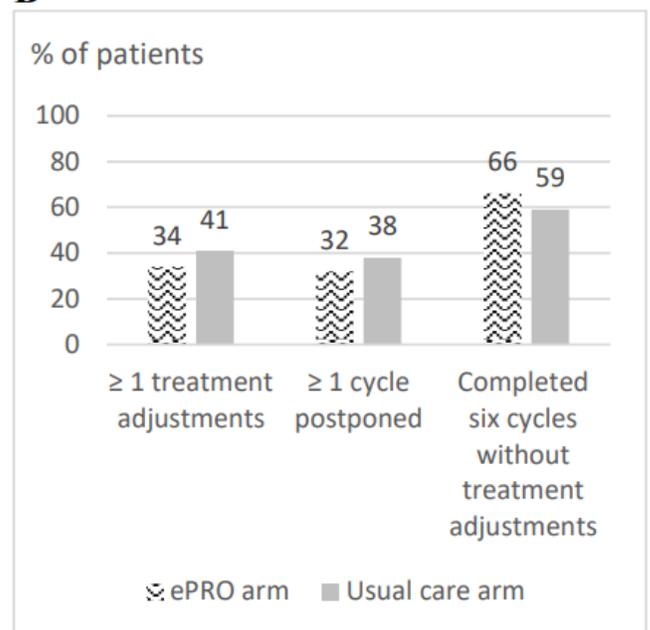


Figure 2

Results. A) Primary results regarding treatment adjustments, hospitalization and febrile neutropenia. B) Descriptive results regarding treatment adjustments, postponement of chemotherapy and completion of full treatment schedule.