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Adapting an Evidence-Based Intervention to Address Targeted Therapy-Related Fatigue in Chronic Myeloid Leukemia Patients

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Abstract

Background—Fatigue is one of the most important quality of life issues experienced by patients being treated with oral targeted therapy for chronic myeloid leukemia (CML). Yet, no intervention exists that specifically addresses strategies to reduce targeted therapy-related fatigue.

Objective—This study adapted an evidence-based clinic-delivered intervention (EBI) ‘*cognitive behavior therapy for post-cancer fatigue*’ for use in CML patients. The existing EBI was based on six established perpetuating factors of fatigue (i.e., Sleep, Activity, Helpful Thinking, Coping with Cancer, Social Support, Fear of Disease Recurrence). Study aims were to gauge reactions to (1) existing content and (2) a new Internet-assisted intervention delivery format.

Methods—Guided by the ADAPT-ITT framework, we used a series of systematic steps and adaptation methodologies, including semi-structured interviews with CML patients and providers, and feedback from topical experts.

Results—Patients were receptive to existing content topics and an Internet-assisted delivery format was acceptable. A key theme reflected the need for a new customized psycho educational module about CML as a disease and its treatment. Both providers and patients held positive views about the potential of the adapted EBI to improve fatigue.

Conclusions—Findings offered essential guidance for the adaptation and reinforced the utility of the adapted intervention.

Implications for Practice—Adapting existing EBI’s for new audiences contributes to advancing findings of evidence-based research, ultimately providing nurses and other health care providers with important referral options to interventions that may provide useful strategies to improve quality of life and reduce targeted therapy-related fatigue.

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Conflicts of Interest

The authors have no conflict of interest to disclose.

Keywords

Chronic Myeloid Leukemia; Quality of Life; Fatigue; Adaptation; Cognitive Behavior Therapy

Introduction

Survival in patients with chronic myeloid leukemia (CML) improved considerably following the introduction of the first tyrosine kinase inhibitor (TKI) imatinib.¹ Although TKIs revolutionized treatment of chronic phase CML, they may need to be taken indefinitely and on a daily basis.² Accordingly, with the growing use of maintenance therapy in certain forms of cancer, CML has become a chronic condition. The transition from short-term active treatment to potentially lifelong maintenance treatment brings attention to finding ways to manage common side effects such as fatigue and pain. Although evidence-based interventions for managing these side effects are available for cancer patients during or after short-term active treatment,^{3, 4} they are not designed for and have not been tested for efficacy in the expanding number of patients who are receiving maintenance treatment with TKIs.

To address the need for an intervention that supports CML patients in managing their health during maintenance TKI treatment, we have built upon a previously empirically supported version of a therapist-delivered cognitive behavioral program for disease-free cancer patients⁵ that specifically addresses one of the most common and debilitating side effects, that is *fatigue*. In this paper, we describe processes used to adapt an existing evidence-based intervention for application in CML patients with targeted therapy-related fatigue. Beyond this immediate goal, the current report seeks to illustrate an approach that can be applied to other existing evidence-based interventions for improving the lives of cancer patients.

As background, fatigue proves to be one of the five most severe side effects in CML patients who are prescribed TKIs, alongside drowsiness, disturbed sleep, muscle soreness and cramping, and trouble remembering things, with one-third of patients reporting persistent moderate-to-severe symptoms.⁶ Additionally, compared to age-matched controls with no history of cancer, patients with CML who take a TKI report significantly worse fatigue severity and fatigue interference.⁷ Moreover, fatigue is the most important factor that limits quality of life of CML patients.⁸ Treatment of fatigue is particularly relevant as chronic side effects may affect adherence to TKI treatment, and adherence is a critical factor to ensure appropriate molecular responses.⁹

Despite the acknowledged importance of this symptom, there are no published intervention studies addressing targeted therapy-related fatigue. However, previous research has demonstrated the efficacy of cognitive behavior therapy (CBT) designed for treating post-cancer fatigue.^{5, 10} The conceptual framework for the intervention developed by the Expert Center for Chronic Fatigue (Nijmegen, The Netherlands) is a model that distinguishes factors that precipitate fatigue from factors that perpetuate fatigue.¹¹ The underlying assumption is that cancer treatment and/or the disease itself may trigger fatigue (precipitating factors), but that other factors such as sleep disturbance, physical inactivity, and fear of disease recurrence are responsible for the persistence of fatigue (perpetuating

factors). As such, CBT for post-cancer fatigue is a tailored, individual-based, clinic-delivered intervention that itself was adapted from the original CBT for chronic fatigue syndrome developed by the Expert Center for Chronic Fatigue.¹² CBT for post-cancer fatigue sessions cover six possible perpetuating factors (the ‘Modules’): Sleep, Activity, Helpful Thinking, Coping with Cancer, Social Support, and Fear of Disease Recurrence (see Table 1 for a description of existing intervention modules). Evidence supports the efficacy of CBT for post-cancer fatigue in decreasing severe fatigue and functional impairment.^{5, 10} Based on this evidence, it is now among the recommended interventions for addressing fatigue in disease-free cancer survivors in guidelines issued by the American Society of Clinical Oncology.¹³

The current report describes a series of systematic steps and processes to adapt and modify an existing evidence-based intervention in response to the needs of another patient population. The process of modifying an evidence-based intervention without changing the intervention’s core elements and internal logic is often referred to as ‘adaptation’.¹⁴ Instead of starting over and expending scarce resources, adapting existing evidence-based interventions has the potential to accelerate the translation of research into practice, thus providing health care professionals and patients with treatment options for new patient target groups. The adaptation process allows for changing context in terms of structure, intensity, format, metaphors, goals etc., while maintaining essential theoretical fidelity and fit. To guide the adaptation process, we developed a plan drawn from the adaptation literature,^{14–19} our prior experience in creating, transcreating and adapting interventions,^{20–24} the NCI’s Stages in Health Communication Model,²⁵ and the ADAPT-ITT Model.²⁶ Table 2 summarizes our plan modeled after the ADAPT-ITT model that includes 8 phases: (1) Assessment; (2) Decisions on evidence-based intervention selection; (3) Administration – What needs to be adapted; (4) Production; (5) Topical experts; (6) Integration; (7) Training and (8) Testing. This paper focuses primarily on the initial steps and methodologies (1–6), which provided the necessary foundation for informing the adaptation. The details on the training and specific results of the pilot study (steps 7 and 8), once complete, will be reported in the future.

As described in the upcoming sections, the adaptation process described here represents a series of sequential phases and steps that advance an idea in response to a patient need, to a final testing and evaluation phase. In our case, this adaptation was predicated on the need for an intervention that offered strategies for patients with CML to ameliorate targeted therapy-related fatigue. The adaptation described here also involves moving from a clinic-based face-to-face delivery during a 6-month period (bi-weekly sessions) to Internet-assisted delivery format using video telephony and tablet computer technology (i.e. FaceTime using iPads) during an 18-week period (weekly sessions) to reduce travel burden. Therefore, as part of our adaptation plan, we also sought to gauge CML patients’ interest in, and acceptability of, delivery channel, duration, and frequency of CBT for targeted therapy-related fatigue.

Methods

Phase 1 and 2 - Assessment and Decision

Our approach builds upon a previously effective evidence-based intervention for post-cancer fatigue⁵ and an established patient need.⁸ We were not proposing to develop a *de novo* intervention. Rather, the program builds on an existing intervention comprised of six modules, based on the precipitating-perpetuating model for fatigued disease-free cancer patients.^{5, 10}

Phase 3 - Administration (what needed to be adapted?)

As part of the adaptation process, we conducted in-depth interviews with CML patients and providers. Next, findings were summarized and implications for adaptation of the existing evidence-based intervention were formulated in close collaboration with topical experts (i.e. developers of the original evidence-based intervention). Then, the original therapy manual and training materials were revised through intensive iterative back/forth communications among research members to incorporate feedback from patients and providers.

Participants and Procedures

Eligible patients were 18 years old, able to speak and read English, diagnosed with chronic phase CML, not previously treated for other cancer (except non-melanoma skin cancer) in the past 2 years, under the care of a Moffitt Cancer Center physician, and on a TKI for 3 months. In addition, patients had to report moderate-severe fatigue in the past week as reflected by a Fatigue Symptom Inventory score of 4.²⁷ Patients were excluded if they had a clinical condition or disease (e.g. anemia or multiple sclerosis) that could account for the presence of moderate-severe fatigue. Potential patient participants were identified via review of medical records and appointment schedules by study coordinators. Identified patients were telephoned 1 week before their next appointment to explain study procedures and screened for fatigue. Eligible patients that gave written informed consent were asked to stay after their appointment to be interviewed.

Eligible providers were staff members in the Department of Malignant Hematology at Moffitt Cancer Center who cared for CML patients as a Medical Doctor, Advanced Registered Nurse Practitioner, Physician Assistant, or Registered Nurse. CML patients at Moffitt Cancer Center are treated by a limited sample of providers. Provider participants were identified and then invited for participation via e-mail. Eligible providers that gave written informed consent were scheduled for an interview.

Instrumentation and Data Collection

Preceding the interview, patients provided demographic information (e.g. age, gender, race, ethnicity, marital status, and education) by completing a self-report form. Clinical information (e.g. CML diagnosis date, current TKI start date, and previous TKI [if applicable]) was collected via medical chart review.

Patient and provider semi-structured interview guides were developed by two of the study investigators (PJ and CM) based on relevant literature, their clinical experiences, and

discussion with the topical experts (HK and MG). The guides consisted of questions about: (1) general thoughts about fatigue in relation to TKIs and CML; (2) general thoughts about TKIs and CML (the provider guide had some additional questions to evaluate the type of education provided to patients before the start of TKI therapy); (3) overall reaction to CBT for targeted therapy-related fatigue program; (4) usefulness and ranking of existing modules; (5) other useful topics; and (6) reaction to Internet-assisted delivery channel (i.e. FaceTime using iPads), duration, and frequency of CBT for targeted therapy-related fatigue. To help elicit feedback about the existing six modules, the interviewers had the modules listed on cards. This made it easier to respond to each module one at a time and gather feedback. It also helped to facilitate ranking of the modules in terms of relative importance. New topics were also solicited.

Two behavioral scientists (PJ and CM) with extensive interviewing experience conducted the individual interviews with patients and providers using the interview guides. Regarding the sample size for the patient interviews (n=10), we were guided by the concept of data saturation, which was defined in this study as the point that no new insights or themes were observed.²⁸ Our research team continually assessed the adequacy of this sample in terms of quality, comprehensiveness, and richness of information.²⁹ For example, was there sufficient depth of information to adequately inform the adaptation of the evidence-based intervention and at which point were no new insights observed. In addition to the number of interviews, the team also considered the amount of time spent with each CML patient (up to 60 minutes) when defining data saturation and stopping data collection.³⁰ In terms of health care providers, our sample was defined (and somewhat limited) by the existing number of providers (n=4) at our institution who cared primarily for patients with CML. Albeit small, it was felt that this sample well represented the required perspectives to address potential modifications for the adapted evidence-based intervention. Time spent with providers was approximately 40 minutes. All interviews were audio-recorded and transcribed by a local professional transcriptionist with experience in qualitative health research. Each patient received \$50 and each provider received \$35 for participating. Liberty Institutional Review Board, a central independent review board, approved the study.

Data Analyses

All interviews were transcribed verbatim. Data transcripts were manually coded using directed content analysis techniques to extend and refine existing theory on CBT for post-cancer fatigue to CBT for patients experiencing targeted therapy-related fatigue.³¹ Codes were generated and refined before and during data analysis using a series of iterative processes by two study researchers (HP and CM). First, the researchers created an initial codebook based on a priori (deductive) codes drawn from existing theory, the interview guides and research questions. The researchers then reviewed all transcripts carefully, highlighting all passages that described relevant data. All highlighted passages were coded using the predetermined codes. Any text that could not be coded into one of these initial codes was given a new inductive code (e.g. '*impact of fatigue*' for descriptions of how fatigue impacted areas of daily living).³¹ The same researchers independently hand-coded the transcripts, compared codes, and resolved discrepancies through consensus, to reach an optimal inter-rater agreement (95%).³² The data were summarized through descriptive

summaries and data display matrices, in which supportive and expanded views of the existing CBT for post-cancer fatigue were identified. A summary listing of module content rankings was also included. The authors reviewed, validated, and verified interpretations, and study conclusions via weekly calls with topical experts. Representative, participant responses were selected to illustrate key findings.

Results

Of the initial 12 eligible patients who were approached for participation, one was found ineligible after consent and one declined to be interviewed; consequently, 10 patient interviews were conducted in total. Four providers were approached and consented for participation. The mean age of patient participants was 53 years (range 37 to 70 years), 60% was male, and 70% Caucasian/30% African American. The majority of patients was employed, married and had some college education. The sample included patients with varying disease and treatment duration. Median time since diagnosis was 6.5 years (range 4 months to 10 years) and median time on current TKI was 11 months (range 3 months to 6 years). Ninety percent of patients had used at least one TKI previously. The most frequently used current TKIs were nilotinib (50%) and dasatinib (40%).

Findings from patient and provider interviews

Illustrative quotations from patients and providers are incorporated in the text in *italics*.

THOUGHTS ABOUT PATIENTS' FATIGUE—Patients commonly described fatigue as '*crushing*', being '*worn out*' or '*whipped out*', and having '*zero energy*' or feeling '*dead*'. Some patients related that they '*cannot get out of bed in the morning*' others just '*crash at the end of the day*'. Fatigue impacts patients in a number of ways, most significantly seen in the change or reduction of social, family, and physical activities. In general, patients felt that their family members are supportive and understanding. Patients indicated that they do not often bring up fatigue to their providers. Most patients felt their providers think fatigue is a normal side effect of TKIs.

Providers acknowledged fatigue as a common complaint, reported by an estimated 70% or more of their CML patients. As such, most providers usually follow up on this concern by discussing sleep patterns, encouraging physical activity, or changing TKIs when more side effects are present.

THOUGHTS ABOUT PATIENTS' MEDICATION AND CML—A number of general thoughts about CML emerged. Considering that most patients wished they did not have a form of cancer at all; some patients described feeling very fortunate for having this type of cancer, since they felt '*It's the best one to have*'. Alternatively, some patients felt guilty for doing well and looking so healthy compared to other patients seen at the Cancer Center. They stated that they '*don't look sick*'. Most patients experienced a range of side effects from the TKIs (e.g. fatigue, nausea, diarrhea, joint pain, and muscle cramp), but related no intentional dose skipping as they felt the TKI is '*keeping me alive*' and is their '*life preserver*'. Unintentional dose skipping was reported by patients, mostly forgetting the second evening dose of nilotinib due to falling asleep. An overwhelming majority of patients

clearly attributed their fatigue to the use of TKIs. In fact, only one patient did not specifically attribute fatigue to TKI use per se but rationalized the presence of fatigue with other factors (i.e., unhealthy diet, low level of physical activity, being overweight, and under stress). In addition, this patient explained that it was difficult to indicate whether the fatigue was related to TKI use since *'I have been on a TKI for so many years and then I am ten years older'*.

Providers thought intentional dose skipping due to side effects does occur in a few patients. All providers had the impression that patients attribute their fatigue to TKI use, and they inform patients about fatigue as a known side effect of all TKIs when initiating treatment.

OVERALL REACTION TO CBT FOR TARGETED THERAPY-RELATED FATIGUE

—Patients and providers had a positive attitude toward the intervention; thinking it is *'worthwhile'*, *'great'*, *'a very novel approach'*, and would be *'helpful'* for fatigued patients. Several patients stated that *'It is a good idea'* and one patient further elucidated *'If we can help people out that would be very good, fatigue affects everything.'* Overall, patients were highly positive and expressed being interested in and open to actually using the intervention. One patient preferred simply an email with information, not an intensive interaction with a therapist using video-telephony.

USEFULNESS AND RANKING OF THE EXISTING MODULES—The majority of patients considered all six modules highly useful. The module *Sleep* currently applied to almost all patients, with waking up too early, falling asleep during the day, or not being able to sleep at bedtime being commonly reported. The module *Activity* applied to all but one patient. Patients experienced reduced or fluctuating activity patterns and considered this module highly pertinent. Most patients reported that the module *Helpful Thinking* about fatigue was not as applicable to them. Some patients did have hopeless thoughts such as *'There is nothing I can do'* and *'I just need to accept it'*, but these thoughts did not seem to impact their everyday functioning. There were a variety of reactions when patients were asked about the module *Coping with Cancer*. More than half of the patients had no major concerns, accepting their situation and saying *'It is what it is'*. Yet, many identified that some thoughts and emotions were triggered before 3-monthly monitoring visits or in case of bad lab results. Reactions from patients who did report concerns ranged from *'Why do I have this disease?'* and *'How would I cope with it if I ever get to the point where it gets really bad'*, to struggling with knowing that not taking the TKI would make them feel better but worsen their disease status. A few struggled with integrating the strict medication regimen into daily life. Although the majority of patients indicated already receiving good support, they did consider the module *Social Support* a useful topic to discuss. A few patients reported changes in social support (e.g. people distancing from them) or unpleasant social interactions (e.g. being called *'lazy'* when they were just too tired to do things). The majority of patients did not experience current issues that would be addressed in the module *Fear of Disease Recurrence*, but felt the module could be useful for others. In fact, patients found the term *'disease recurrence'* confusing and instead referred to *'increased disease activity'*. An explanation for this is that a response evaluation in CML is determined by the value of a molecular marker (i.e. BCR-ABL transcript), instead of determining *'recurrence'*

of a solid tumor in patients of the original evidence-based intervention's population. CML is often considered a slowly progressing disease with long periods of stability. Hence, the terms and language used needed to be edited to better reflect the experience of patients with CML. Even though most patients felt their disease was well controlled and felt that they did not currently need this module, thoughts about increasing disease activity did occur once in a while, mostly triggered by medical appointments or upcoming blood tests. However, some patients worried more about their future health. One patient stated *'Ever since I was diagnosed, I'm waiting for the other shoe to drop'* and later on *'For the first couple years I really did feel that, I had maybe a short period of time, I didn't think that I would live that long and so that was a concern and it certainly impacted the way I was living my life'*. Another patient expressed having thoughts about increase in disease activity all the time, especially after the last switch of TKIs, and expressed *'I still have people who depend on me'*. One patient mentioned the scary aspect of *'dying at a young age'*. In summary, the majority of patients felt all the topics were important for inclusion in the intervention, but the highest priority ones were identified as: Activity, Sleep, and Coping with Cancer. If any module did not apply to them now, all were open to future discussions.

In all, providers considered the content of the six modules useful. One provider did not recognize disrupted sleep/wake patterns as a problematic issue within this patient group. Reactions to the usefulness of the module on fear of disease recurrence (or *'increased disease activity'*) varied among the providers. Some providers thought the content of this module would be more helpful for patients that needed to switch TKIs as a result of increased disease activity compared to patients with stable disease. In addition, one provider wondered about patients' understanding of treatment response and stated: *'the tests that we use to measure whether they are having a good response are very confusing to patients. It's a lot of technical lingo.'* According to providers, the most relevant topics were Activity, Helpful Thinking, and Sleep/Coping with Cancer, with the latter two topics being ranked equally.

OTHER USEFUL TOPICS—Patients mentioned several suggestions for additional topics, including more information on CML and TKIs, nutrition, and impact of CML and fatigue on personal relationships. Providers considered general information about CML and TKIs potentially useful, suggested support groups for fatigued CML patients, and raised fertility issues in younger patients. Some of these topics may be useful in other patient education venues outside of the current intervention.

REACTIONS TO INTERNET-ASSISTED DELIVERY, DURATION, AND FREQUENCY OF CBT FOR TARGETED THERAPY-RELATED FATIGUE—Overall, patients were very receptive to intervention delivery via video-telephony (i.e. FaceTime using iPads). Duration and frequency of CBT for targeted therapy-related fatigue (i.e. 18 weeks, weekly sessions) was acceptable to patients. All patients were familiar with the Internet; most were daily users. One patient expressed a preference to meet the therapist in-person prior to starting the Internet-assisted intervention. Providers had some mixed feelings from a technology perspective; it was thought that older patients might be less receptive to the Internet-assisted delivery channel. However, we found no differences in the views of

younger and older patients regarding their acceptability and interest in the Internet-assisted delivery channel.

Phases 4, 5 and 6 – Production, Topical Experts and Integration

Data and information obtained from the interviews were used to draft a creative brief. A creative brief is a well-identified summary/blueprint of findings that helps to inform the adaptation of the intervention. Table 3 displays the summary of interview findings with adaptation implications and was used to guide the modifications. The goal was to create a therapy manual for therapists that described the process of CBT as applied to patients with targeted therapy-related fatigue and CML and to provide a description of what should be covered in each module. The research team and topical experts (i.e. study consultants who had developed the original evidence-based intervention) then began integrating findings into the therapy manual. The original therapy manual consists of several components: the first section gives an introduction to CRF, followed by an explanation of the model of perpetuating factors, a section on diagnostic measures for each perpetuating factor, and separate sections describing the content of each module. The research team and topical experts had weekly conference calls over a 16-week period to examine each component of the original manual to identify areas to modify, delete, or adapt content based on feedback from the patients and providers. For example, replacing ‘*fear of disease recurrence*’ with ‘*fear of increased disease activity*’. In addition, not all existing case vignettes and quotes in the therapy manual (original vignettes were geared toward disease-free cancer patients) were pertinent for CML patients. Therefore, these were replaced with vignettes and quotations derived from the interviews that better reflected everyday experiences of CML patients. Feedback about the proposed Internet-assisted delivery channel (i.e. FaceTime using iPads) from patients and providers was generally positive. Some providers felt that elderly patients might be less receptive to Internet-assisted delivery, but previous studies indicated that elderly (cancer) patients appear to participate readily in Internet-assisted self-management programs.^{33, 34} Furthermore, no differences were found between younger and older patients in our sample with regard to openness to Internet-assisted intervention delivery, if they were given instructions. Based on discussion with the topical experts and due to a comment by one of the patients, the first intervention session would be delivered in-person to facilitate therapeutic alliance.

Phases 7 and 8 - Training and Testing

Once the therapy manual was finalized, the topical experts created and delivered a 3-day in-person training to prepare two therapists for delivering the intervention (HK and HP). This training included both theoretical background and rationale for each of the intervention modules, familiarizing therapists with intervention delivery, role playing with simulated patients, and discussing video recordings of provider-simulated patients’ interactions with feedback from a topical expert. The testing of the Internet-delivered CBT for targeted therapy-related fatigue is currently being evaluated in a pilot RCT conducted to determine if the intervention can effectively reduce fatigue in patients receiving maintenance treatment for CML.

Discussion

The success of targeted therapy in cancer has improved the overall survival of CML significantly and transformed CML to a chronic disease. Yet many patients suffer from targeted therapy-related fatigue. Thus, an Internet-assisted intervention titled '*Cognitive Behavior Therapy for Targeted Therapy-Related Fatigue*' was developed through an adaptation process to address this need. In general, patients and health care providers felt that all existing modules were relevant (to varying degrees), and had the potential to improve patients' fatigue while on maintenance TKI treatment.

Our results underscore the importance of a patient-tailored approach of selecting intervention modules. In CBT for targeted therapy-related fatigue, therefore, diagnostic assessment instruments will be used to determine which modules should be included and enhanced in the CBT for a particular patient. The CBT will vary only in which modules will be addressed, but within each module the therapy is standardized. For example, the module on fear of increased disease activity only pertained to a minority subset of patients; as such not all patients will receive that module as part of the intervention. Further, although the standard term in the literature '*fear of disease recurrence*' typically applies to patients who have completed treatment for early-stage solid malignancies, patients suggested changing this term to '*fear of increased disease activity*', an issue more relevant to patients who are on maintenance treatment to control their disease.

Our study suggested that patients had a need for more information about their disease and treatment. Therefore, the most significant change to the existing therapy manual was the development of a new psycho-education module '*understanding CML and TKI treatment*' to address this need. This module gauges patients' overall understanding of their disease and treatment, together with a better acceptance of the long-term nature of the treatment needed. An interactive approach was determined to be most suitable for this module. Patients are asked questions about their understanding of CML and its treatment, and the therapist checks or verifies whether this accords with general factual knowledge. Content accuracy was guided by Guidelines Insights for CML from the National Comprehensive Cancer Network,² patient information material about CML from the American Cancer Society,³⁵ and peer-reviewed literature.³⁶ If patients have further questions, they would be referred to their health care provider.

The current study confirmed the utility of using a systematic process for adapting an evidence-based intervention. In particular, the use of the ADAPT-ITT model provided a number of features that allowed for ongoing input from multiple key stakeholders (i.e. patients, providers, topical experts, and research team members). However, we note that due to the nature of the formative research among patients with CML, we only interviewed a relatively small sample of participants from a single comprehensive cancer center. The sample of 4 health care providers at one institution, albeit limited perspectives, offers an exceedingly important snapshot of the views of nurses and other health care providers who primarily care for and are highly familiar with the needs and concerns of patients with CML. In this study, the adaptation process was greatly enriched by the topical experts who had developed the 'original' evidence-based intervention, and their involvement was a significant

strength to the process. Not only was their input essential in the development of the adapted therapy modules and manual, but their engagement also enabled us to train therapists in-person on how to deliver the core elements of the adapted intervention. We have provided further tips in Table 4, which might be helpful for researchers interested in undertaking similar adaptations of existing evidence-based interventions.

Overall, the use of a systematic process for adaptation allowed us to systematically track and pinpoint content areas that should remain the same as well as direct areas to be further customized and modified. Most importantly, it offered the research team a highly fluid and flexible blueprint for documenting the adaptation procedures.²⁶ Our results provide evidence that CML patients have a need for more information on their disease and treatment. As CML is transforming into a chronic illness, practitioners should be aware that it is important for patients to better understand their disease and the way their response is monitored. This might help patients in better understanding and adjusting to the long-term nature of their treatment. The Internet-assisted delivery channel of the intervention appears to be a suitable and flexible vehicle to disseminate information for CML patients while reducing travel burden. The pilot RCT will be useful to supplement the preliminary findings on acceptability of Internet-assisted intervention delivery reported in this study.

Our results set the stage for the pilot RCT (currently underway) that is evaluating the usability, feasibility and efficacy of the adapted CBT for targeted therapy-related fatigue. Ultimately, if proven effective, this will provide nurses and other health care professionals with important referral options to interventions offering practical and patient-tailored strategies to address the most important factor limiting quality of life of CML patients treated with TKIs. In summary, this work provides a strong foundation for addressing a major treatment consequence in the growing population of patients for whom targeted therapies are transforming cancer from a life threatening to a chronic illness.

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References

1. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006; 355(23):2408–2417. [PubMed: 17151364]
2. O'Brien S, Radich JP, Abboud CN, et al. Chronic Myelogenous Leukemia, Version 1.2014. *J Natl Compr Canc Netw*. 2013; 11(11):1327–1340. [PubMed: 24225967]
3. Mock V. Evidence-based treatment for cancer-related fatigue. *J Natl Cancer Inst Monogr*. 2004; 32:112–118.
4. Devine EC. Meta-analysis of the effect of psychoeducational interventions on pain in adults with cancer. *Oncol Nurs Forum*. 2003; 30(1):75–89. [PubMed: 12515986]

5. Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*. 2006; 24(30):4882–4887. [PubMed: 17050873]
6. Williams LA, Garcia Gonzalez AG, Ault P, et al. Measuring the symptom burden associated with the treatment of chronic myeloid leukemia. *Blood*. 2013; 122(5):641–647. [PubMed: 23777764]
7. Phillips KM, Pinilla-Ibarz J, Sotomayor E, et al. Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison. *Support Care Cancer*. 2013; 21(4):1097–1103. [PubMed: 23179489]
8. Efficace F, Baccarani M, Breccia M, et al. Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. *Leukemia*. 2013; 27(7):1511–1519. [PubMed: 23417029]
9. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010; 28(14):2381–2388. [PubMed: 20385986]
10. Prinsen H, Bleijenberg G, Heijmen L, et al. The role of physical activity and physical fitness in postcancer fatigue: a randomized controlled trial. *Support Care Cancer*. 2013; 21(8):2279–2288. [PubMed: 23519566]
11. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol*. 2002; 13(4):589–598. [PubMed: 12056710]
12. Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet*. 2001; 357(9259):841–847. [PubMed: 11265953]
13. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*. 2014; 32(17):1840–1850. [PubMed: 24733803]
14. Card JJ, Solomon J, Cunningham SD. How to adapt effective programs for use in new contexts. *Health Promot Pract*. 2011; 12(1):25–35. [PubMed: 19858321]
15. Barrera M Jr, Castro FG, Strycker LA, Toobert DJ. Cultural adaptations of behavioral health interventions: a progress report. *J Consult Clin Psychol*. 2013; 81(2):196–205. [PubMed: 22289132]
16. Castro FG, Barrera M Jr, Martinez CR Jr. The cultural adaptation of prevention interventions: resolving tensions between fidelity and fit. *Prev Sci*. 2004; 5(1):41–45. [PubMed: 15058911]
17. Resnicow K, Baranowski T, Ahluwalia JS, Braithwaite RL. Cultural sensitivity in public health: defined and demystified. *Ethn Dis*. 1999; 9(1):10–21. [PubMed: 10355471]
18. Solomon J, Card JJ, Malow RM. Adapting efficacious interventions: advancing translational research in HIV prevention. *Eval Health Prof*. 2006; 29(2):162–194. [PubMed: 16645183]
19. Chen EK, Reid MC, Parker SJ, Pillemer K. Tailoring evidence-based interventions for new populations: a method for program adaptation through community engagement. *Eval Health Prof*. 2013; 36(1):73–92. [PubMed: 22523308]
20. Jacobsen PB, Wells KJ, Meade CD, et al. Effects of a brief multimedia psychoeducational intervention on the attitudes and interest of patients with cancer regarding clinical trial participation: a multicenter randomized controlled trial. *J Clin Oncol*. 2012; 30(20):2516–2521. [PubMed: 22614993]
21. Wells KJ, Quinn GP, Meade CD, et al. Development of a cancer clinical trials multi-media intervention: clinical trials: are they right for you? *Patient Educ Couns*. 2012; 88(2):232–240. [PubMed: 22525803]
22. Simmons VN, Quinn G, Litvin EB, et al. Transcreation of validated smoking relapse-prevention booklets for use with Hispanic populations. *J Health Care Poor Underserved*. 2011; 22(3):886–893. [PubMed: 21841285]
23. Quinn G, Ellison BB, Meade C, et al. Adapting smoking relapse-prevention materials for pregnant and postpartum women: formative research. *Matern Child Health J*. 2006; 10(3):235–245. [PubMed: 16341911]

24. Jacobsen PB, Meade CD, Stein KD, et al. Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. *J Clin Oncol*. 2002; 20(12):2851–2862. [PubMed: 12065562]
25. U.S. Department of Health and Human Services, National Cancer Institute. Making Health Communications Programs Work (NCI's Pink Book). <http://www.cancer.gov/publications/health-communication/pink-book.pdf>. Accessed May 12, 2016
26. Wingood GM, DiClemente RJ. The ADAPT-ITT model: a novel method of adapting evidence-based HIV Interventions. *J Acquir Immune Defic Syndr*. 2008; 47(Suppl 1):S40–46. [PubMed: 18301133]
27. National Comprehensive Cancer Network. Cancer-related fatigue (version 2.2015). http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf. Accessed May 12, 2016
28. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Methods*. 2006; 18(1):59–82.
29. Fusch PI, Ness LR. Are We There Yet? Data Saturation in Qualitative Research. *The Qualitative Report*. 2015; 20(9):1408–1416.
30. O'Reilly M, Parker N. 'Unsatisfactory Saturation': a critical exploration of the notion of saturated sample sizes in qualitative research. *Qualitative Research*. 2012; 13(2):190–197.
31. Hsieh H, Shannon SE. Three Approaches to Qualitative Content Analysis. *Qualitative Health Research*. 2005; 15(9):1277–1288. [PubMed: 16204405]
32. Patton, MQ. *Qualitative research and evaluation methods*. Thousand Oaks, CA: Sage Publications; 2001.
33. Feil EG, Glasgow RE, Boles S, McKay HG. Who participates in Internet-based self-management programs? A study among novice computer users in a primary care setting. *Diabetes Educ*. 2000; 26(5):806–811. [PubMed: 11140008]
34. Gustafson DH, McTavish F, Hawkins R, et al. Computer support for elderly women with breast cancer. *JAMA*. 1998; 280(15):1305.
35. American Cancer Society. Leukemia-Chronic Myeloid (Myelogenous) Overview. <http://www.cancer.org/acs/groups/cid/documents/webcontent/003057-pdf.pdf>. Accessed May 12, 2016
36. de Almeida MH, Fogliatto L, Couto D. Importance of adherence to BCR-ABL tyrosine-kinase inhibitors in the treatment of chronic myeloid leukemia. *Rev Bras Hematol Hemoter*. 2014; 36(1): 54–59. [PubMed: 24624037]

Table 1

Description of Existing Intervention Modules of the Original Evidence-based Intervention CBT for Post-cancer Fatigue

Module	Content
(1) Sleep	Patients are encouraged to maintain a regular sleep-wake pattern seven days a week with fixed bed and wake-up times and no daytime napping. If needed, attention is paid to additional sleep hygiene practices.
(2) Activity	A distinction can be made between patients with fluctuating patterns of activity (i.e. bursts of activities followed by inactivity) and patients with a pattern of persistent inactivity. First, patients with fluctuating patterns establish a base level by evenly distributing their level of activity over the day. Upon reaching this base level, a graded activity program (e.g. walking) is started. Patients with persistent inactivity will start the graded activity program immediately.
(3) Helpful Thinking	Dysfunctional fatigue-related cognitions ⁵ (e.g. catastrophizing, low self-efficacy, or unhelpful attributions) are discussed and more helpful ways of thinking are taught.
(4) Coping with Cancer	Insufficient coping with cancer and/or its treatment ⁵ is targeted by talking or writing about these experiences (exposure) in order to help patients to process the experiences and improve coping skills.
(5) Social Support	Some patients perceive a discrepancy between actual and desired social support, experience negative social interactions or have unrealistic expectations of others. These patients are helped to instill more realistic expectations toward their social support group and to communicate more assertively with others with respect to their current abilities.
(6) Fear of Disease Recurrence	Some patients experience excessive fear of disease recurrence. Their fears and thoughts are discussed with a focus on how to deal with the uncertainty about their future health. Dysfunctional beliefs ⁵ are challenged and it is discussed how to reduce ruminating about the possibility of disease recurrence.

Abbreviation: CBT, cognitive behavior therapy.

Table 2

Adaptation Plan for CBT for Targeted Therapy-related Fatigue Modeled After ADAPT-ITT

Phases		Methodologies
1.	<u>A</u> ssessment: What is the need?	Conduct needs assessment of CML patient audience. The literature reviewed clearly demonstrates the need to develop an intervention to address targeted therapy-related fatigue.
2.	<u>D</u> ecision: What evidence-based intervention is selected?	Decision to adapt the CBT for post-cancer fatigue. Initial English-language translation of original therapy manual created using services of a professional translator.
3.	<u>A</u> dministration: What needs to be adapted and what added?	Conduct in-depth interviews with CML patients reporting targeted therapy-related fatigue, including response to use of Internet-assisted delivery channel. Conduct in-depth interviews with CML health care providers. Analyze results to inform next steps.
4.	<u>P</u> roduction: How to produce and draft the evidence-based intervention?	Develop adaptation plan and table of modified text and/or new activities. Draft adapted evidence-based intervention and therapy manual to balance fidelity of core elements, underlying conceptual framework, and internal logic pathways. Document adaptations according to content, context, and concepts, language, and persons.
5.	<u>T</u> opical experts: Who are the experts?	Engage topical experts who developed the original CBT for post-cancer fatigue to ensure input, feedback and review of CBT for targeted therapy-related fatigue drafts.
6.	<u>I</u> ntegration: What is going to be included in the adapted evidence-based intervention?	Integrate feedback and data from topical experts. Draft new CBT for targeted therapy-related fatigue therapy manual and program components with attention to fidelity, fit and congruence to original evidence-based intervention. Review findings with topical experts and make final decisions and revisions. Finalize measures to be used to assess perpetuating factors.
7.	<u>T</u> rainning	Training of staff to implement CBT for targeted therapy-related fatigue involves the therapists reviewing the CBT therapy manual and rehearsing intervention elements in modeling and role-playing sessions with simulated patients. This 3-day in-person training was created and delivered by the topical experts.
8.	<u>T</u> esting: Was the adaptation successful?	Test adapted CBT for targeted therapy-related fatigue and evaluate efficacy in ongoing pilot randomized controlled trial.

Abbreviations: CBT, cognitive behavior therapy; CML, chronic myeloid leukemia.

Table 3

Summary of Findings and Adaptation Implications for CBT for Targeted Therapy-related Fatigue

Interview Findings	Implication(s) for Adaptation
Thoughts about patients' fatigue	
<ul style="list-style-type: none"> Fatigue is described as 'crushing', being 'worn out', being 'whipped out', feeling 'dead' or having 'zero energy'. The most significant impact of fatigue is seen in the change or reduction of physical, mental, and/or social activities. 	<ul style="list-style-type: none"> Descriptions are highly congruent with fatigue experienced by cancer survivors. Integrate specific quotations in the CBT for targeted therapy-related fatigue therapy manual to illustrate specific impact of fatigue for the patient with CML.
Thoughts about patients' medication and CML	
<ul style="list-style-type: none"> Patients experience a range of side effects; some of these interfere directly with sleep quality (e.g. PM dose side effects, very early AM dose) or social activities (e.g. fasting requirements before/after intake of TKIs interfering with having dinner with friends). Intentional dose skipping as a result of side effects was not reported by patients. Providers felt that this does occur in some patients. Patients clearly attributed fatigue to TKI use, but are willing to discuss potential perpetuating factors of fatigue ('modules'). Patients reported both positive (i.e. grateful; 'best kind of cancer to have') and negative (i.e. guilt; 'I look so healthy comparably') feelings about having CML. 	<ul style="list-style-type: none"> Discuss individual side effects and patients' perspectives towards TKI during the first intervention sessions. Emphasize to patients that adherence to TKIs is needed during CBT to conclude if CBT for targeted therapy-related fatigue is effective, but increasing adherence itself is not a goal of the current intervention. Retain model of precipitating and perpetuating factors of fatigue as rationale for the intervention. Incorporate and address both ways of looking at CML in the Helpful Thinking module.
Overall reaction to CBT for targeted therapy-related fatigue program	
<ul style="list-style-type: none"> Patients and providers had a positive attitude toward the intervention. 	<ul style="list-style-type: none"> Retain the envisioned program with adaptations for targeted therapy-related fatigue in CML patients.
Usefulness and ranking of the existing intervention modules	
<ul style="list-style-type: none"> Activity, Sleep, and Coping with Cancer Treatment were considered most relevant to patients. Providers considered Sleep, Activity, Helpful Thinking and Coping with Cancer Treatment most relevant. The term 'Fear of Disease Recurrence' does not apply to a high degree due to the chronicity of CML. Thoughts of disease progression occur mostly before 3-monthly monitoring visits or in case of inconsistent lab results. Providers feel that patients who need to switch TKIs due to progression or intolerance experience more anxious feelings. All 6 intervention modules were considered useful by patients and providers, but variation in personal applicability and relevance exists, reinforcing the value of a 'tailored' intervention approach. 	<ul style="list-style-type: none"> Emphasize the existence of a module for Activity, Sleep, and Coping with Cancer treatment in the first intervention session in order to increase patient motivation. Replace 'Fear of Disease Recurrence' with 'Fear of Increased Disease Activity'. Address coping strategies within Fear of Disease Recurrence module. Careful attention for this topic in patients who have switched TKIs multiple times. Retain all 6 intervention modules and continue tailoring of indicated modules to each participant. Incorporate specific quotations in the CBT for targeted therapy-related fatigue therapy manual to illustrate specific impact on CML patients and draw examples for the proposed case vignettes.
Other useful topics	
<ul style="list-style-type: none"> Patients wanted to receive more information about CML and TKIs. Providers indicated that the tests they use to measure treatment response are quite difficult to understand for patients. Some patients had difficulties with distinguishing normal fatigue from targeted therapy-related fatigue. Some patients experienced intimacy issues and/or mood swings and irritability due to fatigue. 	<ul style="list-style-type: none"> Add new psycho education module '<i>understanding CML and TKI treatment</i>' focusing on understanding of their disease, medication, and monitoring of disease and treatment response. Retain as one of the interventional aims; normalize the experience of 'healthy' fatigue. Both topics are known secondary symptoms of fatigue and will be discussed during the first or second intervention session, if applicable.

Interview Findings	Implication(s) for Adaptation
<ul style="list-style-type: none"> • Impact of patients' fatigue and impairments on significant others. • Balancing several life domains with a limited energy level. • Nutritional concerns (e.g. lack of appetite, fasting requirements). 	<ul style="list-style-type: none"> • Retain the element of having significant other attend at least one session to explain aim and rationale of intervention. • Retain the variation in activities in several domains addressed in the Activity module. • No implications for adaptation, this is not a part of the current intervention, but may be useful in other patient education venues.
Reaction to Internet-assisted delivery, duration, and frequency of CBT for targeted therapy-related fatigue	
<ul style="list-style-type: none"> • All participants were familiar with using the Internet and receptive to CBT for targeted therapy-related fatigue delivery via video telephony. • Frequency and duration of CBT for targeted therapy-related fatigue were acceptable to participants. • Patients expressed different preferences with respect to timing of the weekly sessions. • One participant preferred meeting the therapists in person first, before start of video telephony delivery of CBT for targeted therapy-related fatigue. • Providers had some reservations with respect to delivery channel in the elderly patients, due to technology aspects 	<ul style="list-style-type: none"> • Maintain intended use of video telephony (i.e. FaceTime) for intervention delivery. • Retain frequency and duration of CBT for targeted therapy-related fatigue. • Incorporate flexibility in scheduling of weekly sessions (morning, afternoon, evening, weekends). • First intervention session with the therapists will be done in person at the treatment facility, contrary to our plans to shift completely to an Internet-assisted delivery. • Incorporate on-site instructions and testing of FaceTime following the first intervention session for all patients. Have a contact person available for patients during the intervention period.

Abbreviations: CBT, cognitive behavior therapy; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Table 4**Tips for Researchers Interested in Undertaking Similar Adaptations of an Existing Evidence-based Intervention**

Researchers might find the following tips helpful:

- Upon initiating a project, form a collaborative professional relationship with the original intervention developers and clinicians who have experience with delivering the intervention. Ask them to be part of the team.
- Adhere to systematic and iterative steps that guide the adaptation process driven by initial need for the intervention through the final testing of the adapted intervention. This provides an adaptation blueprint that endorses relevancy, rigor and meaning.
- Establish a multidisciplinary team (local, national or international) to ensure inclusion of varied perspectives and who bring content-specific knowledge, methodological, and theoretical expertise. This might include well-versed researchers with backgrounds in psychology, nursing, and education as well as providers who care for the patient group. Include a team member with experience in developing and/or adapting interventions or education programs.
- Engage key stakeholders such as patient and providers to make adaptations to ensure the ecological validity of the intervention, while still maintaining fidelity to the intervention's core elements.
- Maintain a robust and consistent communication plan with study team members to ensure discussions and decisions about adaptation adjustments.
- Finally, carefully document processes and justify modifications of the intervention protocol to monitor success, and revisions of the adapted components.