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Summarized



Adherence to treatment and side effect management in breast cancer

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Breast cancer is the most common cancer among women across the world. In developed countries, recent years have seen dramatic improvements in survival rates for women living with this condition, which has been attributed to widespread screening and improved treatment. The success of such treatment is dependent on a high level of adherence, however it is surprisingly common for women with breast cancer to miss doses or stop taking their preventative treatment altogether.

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Executive Summary

The success of treatments for breast cancer is dependent on a high level of adherence.

Sub-optimal adherence compromises the benefit of treatment and increases healthcare costs. For example, improved adherence to hormone therapy could prevent over 400 deaths in the UK each year and save the healthcare system £30 million.

Factors contributing to non-adherence are complex and vary between individuals. Predictors of non-adherence include experience of side effects, concerns about treatment, doubts about the benefits of treatment and a lack of confidence in the ability

to adhere. Features of the healthcare system, including the relationship between healthcare professionals and patients, the quality of the consultation, and degree of patient involvement in treatment decisions are also important.

There have been few evaluations of strategies to facilitate adherence to treatments for breast cancer. Promising interventions have been multidimensional, including patient education, practical strategies, support and follow-up. The systematic development and evaluation of individually tailored interventions that target barriers to adherence remains a priority for future research.

“Improved adherence to hormone therapy could prevent over 400 deaths in the UK each year and save the healthcare system £30 million”

Introduction

Breast cancer is the most common cancer among women worldwide, leading to almost half a million deaths per year [1]. While incidence of breast cancer is increasing, [2] survival rates have improved dramatically in developed countries. For example, ten year survival rates in the UK increased from 54% for those diagnosed in the early 1990s to 77% for those diagnosed in 2005-2009 [3].

Increased survival has been attributed to a combination of factors including population based screening and improved treatment [4]. Recommended treatments may include surgery, radiotherapy, chemotherapy, hormone therapy (e.g. tamoxifen, anastrozole), biological therapy (e.g. trastuzumab) and bisphosphonate therapy, depending on the specific nature of the breast cancer (e.g. stage, grade, cancer cell proteins) [2, 5-7]. Further tailoring of treatment according to an individual's genetic profile is a current area of research and development [8].

Medications prescribed for breast cancer have a range of side effects that may require monitoring and management. For example, hormone therapy can lead to cardiovascular, musculoskeletal and gynaecological side effects, as well as hot flushes, reduced libido and cognitive dysfunction [9]. While these are generally mild to moderate in severity, they are common and can have a major impact on the quality of life of women taking these treatments. Indeed, analysis of messages posted about aromatase inhibitors on internet forums revealed that almost 1 in 5 posts referred to side effects (most commonly musculoskeletal pain and vasomotor symptoms such as sweating and hot flushes)[10]. Other breast cancer treatments can have serious adverse effects, such as cardiac dysfunction associated with trastuzumab, which needs careful monitoring [11].

The success of treatment for breast cancer is dependent on patients taking medications in the way they are prescribed. For women prescribed hormone therapy, this means

taking treatment for an extended period of time: while current guidelines recommend treatment should be taken for five years, recent research suggests that this should be extended to ten years [12, 13]. The importance of adherence to hormone therapy for survival was demonstrated in an observational study of over 8,000 women with breast cancer [14]. Ten year survival rates were significantly lower among those who discontinued treatment early or took less than 80% of the prescribed doses compared to those who took the treatment as prescribed.

Despite the importance of adherence, research suggests that women with breast cancer often experience difficulty in taking their medication as prescribed. To date, the majority of published research has been conducted with women taking hormone therapies. A recent analysis of pooled data from 26 studies estimated that 14% of women discontinue endocrine therapies within 1 year, increasing to 41% by 5 years. Among those who remain on treatment, 20% of women take less of their medication than prescribed at 1 year increasing to 32% by five years [15]. Studies reporting on adherence to other treatments for breast cancer are scarce, however, suboptimal rates of adherence to oral chemotherapy[16]; trastuzumab [17] and bisphosphonates [18] have been reported.

The cost of non-adherence to breast cancer treatments is high. A recent economic evaluation of adherence to tamoxifen found that women classified as low adherers typically lost approximately 1.12 Quality Adjusted Life Years (QALYs) compared to high adherers and cost the healthcare system almost £6,000 more than patients who took the treatment as prescribed [19]. Overall this study suggests that improved adherence to tamoxifen could prevent over 400 deaths and save over £30 million in healthcare costs each year in the UK, highlighting the need to develop effective interventions to help women take their hormone therapy correctly.

41%
 of women discontinue endocrine therapies before 5 years on treatment, with 14% discontinuing within only 1 year.

Patient insights

Marie* spoke to us about her experience of treatment for breast cancer. In 2002, Marie was diagnosed with breast cancer and underwent a mastectomy, chemotherapy and radiotherapy, followed by hormone therapy (tamoxifen) for five years.

In 2009, she discovered that she had secondary cancers in her ovaries, liver, lungs, hip, spine and central nervous system.

Following further surgery, chemotherapy and radiotherapy, Marie is now prescribed a hormone therapy (anastrozole), an oral bisphosphonate and trastuzumab. Her cancer is currently stable.

Marie reported having a dilemma when first prescribed trastuzumab. While she felt fortunate to be offered this expensive drug, she had concerns about the potential effects of this medication on her heart. This concern was particularly salient because her friend had died of a heart attack after taking trastuzumab for breast cancer. Marie described how discussion with her oncology specialist helped to allay her concerns.

DISCUSSION WITH HEALTH PROFESSIONALS REGARDING CONCERNS

“I talked through my issues with the specialist and they explained that they now monitor the heart with scans every three months and then I felt more reassured.”

Feedback from regular scans to monitor her cancer has given Marie confidence that trastuzumab is currently working for her

PERCEIVED NEED FOR TRASTUZUMAB

“Since I've been on the Herceptin [trastuzumab], the cancer has been stable, so I think it's the Herceptin [trastuzumab] that's slowing things down and keeping me alive.”

She was less convinced of the importance of her prescribed hormone therapy, because her previous experience of tamoxifen had not prevented secondary cancers from developing:

UNCERTAIN ABOUT EFFICACY OF HORMONE THERAPY

“I'm not quite sure about Arimidex [anastrozole] because when I was first diagnosed I went on tamoxifen for five years - whether that kept the secondaries at bay for five years and they developed in the two years after

I'd stopped, or whether they were developing all the time, I just don't know.”

Marie reported that she had excellent support and information to help her manage her condition. She valued having easy access to specialist health professionals:

ACCESS TO SPECIALIST INFORMATION AND ADVICE

“If I'm not sure about anything or I've got concerns, rather than go to the GP, I phone the breast care nurses and they give good advice.”

Marie emphasised the importance of being able to provide support and advice for other people with breast cancer and felt that she had benefited from the support of others who had experienced breast cancer first-hand, for example, when considering a new treatment:

HAVING REALISTIC EXPECTATIONS OF TREATMENT

“I know a lot of people now through breast cancer and it's always good to talk to someone - if you change your drug, there's always someone you can ring and say 'You've been on that - how was it?'”

Marie described how adjusting to a new medication sometimes took time, but then became a part of her life.

ADJUSTING TO A NEW MEDICATION REGIMEN

“When you take the bisphosphonate tablet in the morning you have to take it with a huge glass of water and then be upright for an hour and not eat or drink. It was inconvenient at first but now it's become a way of life - it's just something I do every morning.”

Going to hospital every three weeks for trastuzumab treatment had become part of Marie's routine. She emphasised the importance planning her life around this:

PLANNING AROUND TREATMENT

“You have to just plan. Whenever anyone asks me to do anything I have to check the diary - I can't go anywhere without my diary! I always prioritise my Herceptin [trastuzumab] treatment over other appointments and events.”

While Marie had not experienced significant side effects from her current treatment, she was aware of potential adverse effects. She described taking into account the risks and benefits of treatment:

WEIGHING UP PROS AND CONS OF MEDICATION

“All of these drugs have their side effects but you've got to weigh that up against the benefits.”

* pseudonym

Insights from a leading researcher

We spoke with Professor Annette Stanton, a senior research scientist at the University of California, about her current work developing interventions to facilitate adherence to hormone therapy in breast cancer.

In order to develop effective, evidence-based interventions, Professor Stanton highlighted the importance of first understanding the experiences of women taking these treatments and the factors associated with non-adherence.

In a major project funded by the Breast Cancer Research Foundation, Professor Stanton and her colleagues Professor Keith Petrie (University of Auckland) and Dr Ann Partridge (Harvard Medical School) recruited over 1,000 women who had taken hormone therapy for breast cancer within the previous twelve months. They found interesting differences between those who had persisted with their treatment and those who had stopped prematurely.

“The women who didn’t persist were likely to report depressive symptoms, a poor relationship with their oncologist and more general physical symptoms. They also reported more negative and fewer positive feelings about their hormone therapy.”

In a separate analysis exploring the adherence behaviour of those who persisted with treatment, the researchers found that those who missed more doses also reported a poorer relationship with their oncologist, lower perceived need for hormone therapy and more negative feelings associated with their hormone therapy.

Professor Stanton described how these findings may help health professionals to facilitate adherence to hormone therapy.

“Establishing a collaborative, trusting relationship with the patient is important. There are at least two other ways that health professionals can be helpful.

1. Understanding medication: Women need to understand why the medication is being prescribed and the benefits of the medication. So health professionals could check patients’ understanding of their need for treatment and engage in a discussion about it.

2. Discussing side-effects: It’s very important for health professionals to talk to patients about the possible side effects of treatment and how to manage them.”

She also described the implications of her research for the development of tailored adherence interventions.

“Different women need different things. Some women may truly benefit from some information and education about the importance of medication in terms of survival benefit. Some women may need information on how to deal with the side effects.

Depressed women may need something very different - for example, it may be necessary to directly address their depressive symptoms. We may therefore need a stepped care type of approach, where something very minimal is very effective for some women but something more intensive might be needed for others.”

Predictors of non-adherence

Table 1 summarises some of the key predictors of non-adherence to treatment for breast cancer identified in recent reviews [20-24] according to five categories suggested by the World Health Organization [25]. It should be noted that these reviews

encompass various treatments for breast cancer (e.g. oral chemotherapy, hormone therapies) and different subtypes of non-adherence (e.g. including missed doses and non-persistence with treatment).

TABLE 1: Determinants of non-adherence to breast cancer treatment

Patient related	Concerns about treatment (e.g. adverse effects/ taking treatment over the long term/ inconvenience) Doubts about necessity for treatment or adherence Perceived lack of benefit Lack of confidence in ability to adhere long-term Perceived risks outweigh perceived benefits
Therapy related	Experiencing side effects Taking a greater number of prescription medicines Longer duration of treatment
Illness related	Cancer severity Co-morbidity (including depression) Having undergone a mastectomy (rather than breast-conserving surgery)
Healthcare system	Poor patient/provider relationship No single doctor responsible for follow-up Lack of discussion regarding side effects and adherence
Social and economic	Younger age and older age Lower income/ lower socio-economic status Cost of treatment (more expensive drugs)

While these reviews reveal a wide range of potential reasons for non-adherence, as emphasised by Professor Stanton, it is important to recognise that factors driving non-adherence differ across individuals. It is therefore necessary for health professionals to explore and address

individual beliefs and barriers to adherence. Research has shown that the extent of input and specific types of information desired to make a decision about treatment differ widely between patients, indicating the need for individually tailored information [26].

These findings indicate that promising strategies to enhance adherence to treatment for breast cancer may include:

- Implementation of strategies to detect, report and manage side effects.
- Eliciting and addressing individuals’ beliefs about their treatment including concerns about adverse effects, doubts about need for treatment, and lack of confidence in the ability to adhere.
- Education about the role of anticancer treatments in controlling disease and the rationale for maintaining a high level of adherence.
- Frequent assessment of adherence to proactively identify and address challenges in patients taking long-term treatment.
- Exploring challenges to adherence stemming from co-existing medical conditions.
- Good communication between the patient and healthcare provider.
- Involving patients in decisions about their treatment.

Interventions to enhance adherence

Only two studies have evaluated interventions to improve adherence to hormone therapy among women with breast cancer.

One was a large, randomised study of an intervention to assess the impact of educational materials including written information (letters and brochures), monthly reminders about persistence and low cost gifts including a medication organiser [27].

In the other study, patients were randomly assigned to receive one of three interventions: 1) standard care, 2) motivational letters at pre-defined intervals or 3) telephone calls from a nurse at predefined intervals to remind, inform and motivate patients, provide individualised information and feedback [28]. Both reported statistically non-significant overall findings,

were also improved among these patients, driven by a 40% reduction in outpatient hospital costs compared to the matched control sample. The clinical impact of improved adherence was not, however, assessed in this study. A second pharmacy intervention, had a significant impact on some, but not all, of the aspects of adherence measured [31]. A third study which compared standard packaging of medication with a daily pill box found no significant impact on adherence [32]. The limited effectiveness of these interventions has been attributed to the fact that they were not targeted to those known to be/ at risk of being non-adherent, therefore limiting the potential for improvement [29]. Furthermore, contrary to recommendations [33] these were largely generic 'one size fits all' interventions, rather than tailored to the specific needs and preferences of individuals. In other illness groups, tailored interventions have successfully improved adherence to medication [34-36]

To date there have been no evaluations of interventions to enhance adherence to trastuzumab among patients with breast cancer. Furthermore, many of the predictors

of non-adherence identified in the literature have yet not been addressed in adherence interventions (e.g. depressive symptoms, relationship with health professionals). In addition, given the relationship between the experience of side effects and non-adherence to treatment prescribed for breast cancer, the development of interventions to help patients to manage side effects may be a promising area for future research. Mindfulness-based interventions have been shown to help people manage treatment side effects in other illness groups [34] and preliminary research suggests these interventions may be effective for women with breast cancer [35-37].

although the authors of the second study suggest that the findings may still be clinically significant [28].

A recent systematic review of interventions to enhance adherence to oral chemotherapy [29] identified one study reporting a significant effect of a specialist pharmacy intervention on adherence [30]. This multi-faceted intervention included patient education, adherence screening and reminders, physician input for those with low adherence, telephone counselling and signposting to healthcare providers and resources. Patients receiving this speciality pharmacy programme, including those with breast cancer, had a higher rate of adherence than a matched sample. Financial outcomes

“ Patients receiving this speciality pharmacy programme, including those with breast cancer, had a higher rate of adherence than a matched sample. ”

Concluding statements

Recent years have seen major advances in treatment for breast cancer but the success of these treatments is dependent on adherence. Non-adherence has been associated with increased mortality and higher healthcare costs.

Adherence with treatments for breast cancer is suboptimal. To date, the majority of adherence research has been conducted with women prescribed hormone therapies, where as many as half do not complete their treatment, compromising efficacy and increasing the risk of mortality.

Identifying predictors of non-adherence to different types of treatment for breast cancer is essential in order to develop effective, evidence-based interventions.

Studies have identified modifiable predictors of non-adherence including experience of side effects, beliefs about treatment and the quality of health care consultations, however reasons for non-adherence vary greatly between individuals.

To date few interventions have been developed to enhance adherence to treatment for breast cancer and they have had limited success. Most have focussed on educating patients about their treatments and have not addressed a range of other variables associated with non-adherence, such as the relationship with health care professionals, depressive symptoms, and side effect management.

Furthermore as reasons for non-adherence differ between individuals, interventions should be tailored according to individual needs and preferences. Just as treatments for breast cancer are becoming increasingly personalised, so too should interventions designed to support patients taking them.

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