

## **Breast cancer's easy wins: (1230 words)**

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Despite the steady decline in breast cancer mortality rates over the last 35 years, almost 1,000 women are still dying every month in the UK from this disease, with health inequalities persisting due to age, location and socioeconomic status. The UK is struggling with an increased prevalence of women living with breast cancer and breast cancer survivors who may continue to experience morbidity due to the disease and its treatment. We face mounting financial pressures in the research community and the NHS. To provide more effective, compassionate and cost-effective care we are all under pressure to do more with less. So what are our options?

This question was recently explored in an NCRI Cancer Conference debate hosted by Breast Cancer Now- the UK's largest dedicated breast cancer research charity. A panel of experts, chaired by Professor Judith Bliss, argued whether improving and optimising existing treatments was preferable to the development of new ones. Although more votes ultimately were cast for "newly developed treatments" the panellists pushing for repurposing and more efficient use of current breast cancer treatments swung the most votes.

So how did we overcome the "drug development" side's argument of pipeline research potential to swing so many votes? Our arguments highlighted the issues of high clinical trial attrition rates; poor NICE approval rates; eye watering and ever increasing costs and the huge delays associated with bringing new cancer treatments to market. The crux of our arguments however focused on the many, potentially "easy wins" for patients with breast cancer that could be accomplished with the resources already at our disposal.

### **Doing more with less**

#### **Adjuvant bisphosphonates**

In the last decade we have seen some success stories of repurposing drugs to benefit patients with some types of cancer. One prominent example is the use of bisphosphonates to reduce the risk of distant recurrence in postmenopausal women with early breast cancer (EBC). Bisphosphonates are effective in the treatment of established metastatic bone disease and have been in clinical use for three decades with an acceptable adverse event profile and favourable risk-benefit ratio. Recently these cheap and off-patent drugs have been shown to reduce the risk of breast cancer recurrence, particularly in bone, and improve breast cancer survival in post-menopausal women (1). The early breast cancer trialists' (EBCTCG) July 2015 meta-analysis of the use of bisphosphonates in early breast cancer demonstrated an 18% relative reduction in distant recurrence, a 28% reduction in

bone recurrence and an 18% reduction in breast cancer mortality. These effects were statistically significant, clinically important and realised with the use of very inexpensive drugs.

### **Endocrine therapy**

The optimisation of endocrine therapy also provides scope for improved outcomes. Although it was often stated that patients with EBC were generally compliant with endocrine therapy this has been shown not to be the case. Herschman et al estimated that survival at 10 years was 80.7% for women with breast cancer who continued their endocrine therapy versus 73.6% for those who discontinued ( $P < 0.001$ ) (3). A further study shows that more than half of patients were non-compliant with their treatment to a significant degree and this resulted in a 10% increase in mortality compared to those who took the medication as prescribed. This represents a 25% loss of treatment effectiveness equivalent to the omission of systemic adjuvant therapies in many circumstances. The potential for simple educational interventions to improve adherence, along with a better understanding of the side effects of these treatments and their management could go a long way to improving the efficacy of drugs already in routine use. The potential for extending the use of adjuvant endocrine therapy beyond 5 years with either tamoxifen or aromatase inhibitors has also been demonstrated to modestly reduce recurrence risk and mortality in higher risk patients with ER positive EBC. Toxicity issues may mean that many breast cancer survivors choose not to pursue this option, but the lack of current ability to identify patients who may be candidates for extended endocrine therapy because of restricted follow up protocols is a bigger problem which, in most circumstances, is likely to deny an opportunity for a discussion of the merits and downsides of this approach.

### **Variation in practice**

To do more with less, we must also improve the efficiency of our health service and try to address the great variation in surgical and adjuvant treatments that are used in different breast units. The annual audit of screen-detected breast cancer conducted by the NHS Breast Screening Programme (NHSBSP) in conjunction with the Association of Breast Surgery (ABS) has for many years revealed marked variations in the use of adjuvant therapies, a situation which has been difficult to address and has allowed inequalities to persist. An analysis of data from the Sloane Project has similarly shown a marked variation in the use of radiotherapy after breast conserving surgery for DCIS. These variations need to be addressed to reduce the disparity we see in outcomes across the UK.

### **'Real world' outcomes**

We also have to keep in mind that most decisions about commissioning healthcare and introducing new treatments are made as a result of randomized controlled clinical trials (RCTs). Studies involving 'real world data' have commonly demonstrated that outcomes in routine clinical practice are often worse than the evidence produced by clinical trials would indicate. Toxicities may be worse and exclusion criteria often mean that many patients with comorbidities or complications are not accounted for and do not benefit to the same extent when regimes are applied in the real world. There are limited data comparing 'real world' vs RCT outcomes in metastatic breast cancer and we are consequently missing opportunities to optimize treatments for EBC by a relative failure to systematically collect and analyze these outcomes.

The Systemic Anti-Cancer Therapy (SACT) dataset collated by Public Health England is an ambitious attempt to evaluate the use of systemic therapies for all cancers in England and corresponding patient outcomes. An assessment of factors affecting 30-day mortality following chemotherapy in patients with breast and lung cancer was recently published. The results revealed that several factors affect the risk of early mortality of breast and lung cancer patients in England and that some

groups are at a substantially increased risk of 30-day mortality. These groups of patients with poorer performance status and other factors likely to increase treatment related mortality and morbidity are usually excluded from clinical trials. The collection of 'real world' outcomes may optimize patient selection and avoid the use of some toxic, less effective but expensive therapies.

The importance of collecting and analyzing routine data to complement those available from clinical trials is critical to improve clinical decision making and optimize outcomes. (5).

## Conclusion

**The discovery of new drugs, particularly those targeted to specific pathological molecular targets in breast cancer is important, but it is worth reflecting that currently trastuzumab is the only HER2-targeting drug in routine use as adjuvant therapy and was introduced a decade ago. Other HER2-targeting drugs are available in metastatic disease and as neoadjuvant therapy but there are currently no available targeted drugs beyond those which are specific to the HER2 target in the context of adjuvant therapy. Personalized medicine has much promise but is slow to deliver and costly. There are many opportunities to improve the current management of EBC by the use of bisphosphonates, by the optimisation of endocrine therapy, by more comprehensively analyzing real world outcomes and addressing inequalities in care.**

## References

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