The Development and Translation of Tamoxifen to the Clinic in Manchester

Tamoxifen was developed in the laboratories of ICI Pharmaceuticals in Manchester The first clinical trial of the drug was begun at the Christie Hospital, Manchester in December 1969 and reported in 1971 (Cole et al 1971). This study demonstrated that tamoxifen was considerably less toxic than the oestrogens and androgens in use to treat advanced breast cancer at the time and led to the widespread use of the drug to treat advanced breast cancer but also after surgery for breast cancer (Ribeiro and Palmer 1983) and more recently to prevent breast cancer (Cuzick et al 2002). Subsequent studies in Manchester and elsewhere demonstrated the importance of oestrogen and progesterone receptor content of the tumour for reponse to tamoxifen and overall outcome in patients (Howell A et al 1984,1987). In Manchester we were the first to demonstrate the effectiveness of tamoxifen when given in the weeks before surgery (the first 'window trial') showing a marked reduction in tumour cell proliferation (Baildam et al 1987, Clarke et al 1993, Ellis et al 1997) and later that further responses could be seen after stopping treatment with tamoxifen (the so called 'withdrawal effect'. Howell et al 1992). Subsequent studies were performed to determine whether adding additional treatments to tamoxifen improved responsiveness (Jonat et al 1995 , Fentiman et al 1994, Dowsett M et al 2001, Howell et al 2004).

An overview of all randomised trials (including those from Manchester) where tamoxifen was compared with placebo after surgery for breast cancer indicated that tamoxifen reduced breast cancer relapse by approximately 50% and improved survival by about 30% (Early Breast Cancer Trialists Collaborative Group 2005) and concluded that a large part of the marked improvement in survival after surgery for breast cancer was related to the widespread introduction of tamoxifen treatment (Peto 1998)

In the adjuvant trials it was noted that during treatment the incidence of new cancers in the contralateral breast were reduced by 50% (Cuzick and Baum 1985). This lead to trials of tamoxifen versus placebo as preventive agents in women at high risk of breast cancer (The International Breast International Study I. Howell A CoPI). Overall the results showed a reduction in risk of breast cancer by approximately 40% (Cuzick et al 2002,2007), a preventive effect which was show to last for up to 15 years after the standard five years of treatment with tamoxifen (Cuzick et al 2015) with good quality of life (Fallowfield et al 2001).

Further studies on human normal breast tissue transplanted into immune deprived mice indicated that tamoxifen reduced cell proliferation and increased apoptosis in women at high risk with and without mutations in BRCA1 and BRCA2 (Bramley et al

2006). Other studies in Manchester have lead to a greater understanding of the effects of oestrogen and tamoxifen on the normal breast (Laidlaw et al 1995, Clarke et al 1997, Anderson et al 1998, Clarke et al 2005), and the mechanisms of tamoxifen resistance (Martinez-Outschoorn et al 2011, Simoes et al 2015).

There is a need for markers of responsiveness to tamoxifen in the prevention setting since only just under half of women have a reduction in breast cancer risk. The Manchester group and collaborators have explored the value of nipple secretions (Harding et al 2000) and, more recently the value of reductions in mammographic density as a measure of responsiveness (Warwick et al 2003, Cuzick et al 2011, Donnelly et al 2014) as markers .

Manchester's leading involvement in NICE guidelines led to recommendations in 2013 that tamoxifen was offered to women at high risk and considered in women at moderate risk of breast cancer (Evans 2013). Although women at high risk and thus candidates for tamoxifen use are seen in Family History Clinics they are usually referred by GPs when younger than 50yrs of age (Donnelly et al 2014). We have demonstrated that highrisk older women may be detected in the context of the NHS National Breast Screening Programme and offered preventive tamoxifen s for younger women in Family History Clinics (Evans et al 2014, 2015, 2016). Work in Manchester has shown that full application of NICE guidelines could prevent 35% of 15,000 breast cancers annually in the UK equivalent to a saving in the costs of breast cancer treatment annually of £100,000,000 compared with a preventative treatment such as tamoxifen that only costs about £12 per year.

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