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Original Research

HER2 status predicts for upfront AI benefit: A TRANS-AIOG meta-analysis of 12,129 patients from ATAC, BIG 1-98 and TEAM with centrally determined HER2

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Abstract ***Background:*** A meta-analysis of the effects of HER2 status, specifically within the first 2–3 years of adjuvant endocrine therapy, has the potential to inform patient selection for upfront aromatase inhibitor (AI) therapy or switching strategy tamoxifen followed by AI. The pre-existing standardisation of methodology for HER2 (immunohistochemistry/fluorescence in situ hybridization) facilitates analysis of existing data for this key marker.
Methods: Following a prospectively designed statistical analysis plan, patient data from 3 phase III trials Arimidex, Tamoxifen, Alone or in Combination Trial (ATAC), Breast International Group (BIG) 1-98 and Tamoxifen Exemestane Adjuvant Multicentre Trial (TEAM)] comparing an AI to tamoxifen during the first 2–3 years of adjuvant endocrine treatment were collected and a treatment-by-marker analysis of distant recurrence-free interval-censored at 2–3 years treatment − for HER2 status × AI versus tamoxifen treatment was performed to address the clinical question relating to efficacy of 'upfront' versus 'switch' strategies for AIs.
Results: A prospectively planned, patient-level data meta-analysis across 3 trials demonstrated a significant treatment (AI versus tamoxifen) by marker (HER2) interaction in a multivariate analysis; (interaction hazard ratio [HR] = 1.61, 95% CI 1.01–2.57; $p < 0.05$). Heterogeneity between trials did not reach statistical significance. The HER2 negative (HER2−ve) group gained greater benefit from AI versus tamoxifen (HR = 0.70, 95% CI 0.56–0.87) than the HER2-positive (HER2+ve) group (HR = 1.13, 95% CI 0.75–1.71). However, the small number of HER2+ve cases (n = 1092 across the 3 trials) and distant recurrences (n = 111) may explain heterogeneity between trials.
Conclusions: A patient-level data meta-analysis demonstrated a significant interaction between HER2 status and treatment with AI versus tamoxifen in the first 2–3 years of adjuvant endocrine therapy. Patients with HER2−ve cancers experienced improved outcomes (distant relapse) when treated with upfront AI rather than tamoxifen, whilst patients with HER2+ve cancers fared no better or slightly worse in the first 2–3 years. However, the small number of HER2+ve cancers/events may explain a large degree of heterogeneity in the HER2+ve groups across all 3 trials. Other causes, perhaps related to subtle differences between AIs, cannot be excluded and warrant further exploration.

1. Introduction

For well over 20 years the HER2 (neu/c-erb-b2) oncogene has been associated with resistance to endocrine therapy [1]. As knowledge relating to extended type I receptor tyrosine kinase family (RTK; EGFr, HER2, HER3 and HER4) signalling was developed, functional and clinical evidence substantiating the link between resistance to tamoxifen therapy and type I RTK expression became more extensive [1–3]. A decade ago we suggested that analysis of type I RTKs might be of value in determining which patients were most likely to benefit from aromatase inhibitor (AI) rather than tamoxifen therapy [4]. At this time we made two critical observations relevant for the clinical setting, first, that the impact of HER2 and other type I RTK status on outcome following tamoxifen therapy was time dependent, and second, that HER2 was not the sole driver of tamoxifen resistance in early breast cancer [4,5].

The type I RTK family (HER1–4) form 10 homodimers or heterodimers and are activated by a broad range of ligands leading to a complex inter-relationship between signalling kinases and downstream pathways [3]. There is evidence that HER4 does not promote breast cancer proliferation *in vivo* and is linked to good prognosis in breast cancer patients [4,6]. In contrast, breast tumours expressing HER1, HER2 or HER3 receptors exhibit increased proliferation *in vivo* and are associated with poor outcome [4].

Establishing the impact of specific genes on cancer prognosis in the clinical setting is complicated by multiple factors including; the impact of multimodal