MOLECULAR CHANGES IN LOBULAR BREAST CANCERS IN RESPONSE TO NEOADJUVANT LETROZOLE

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Background: Invasive lobular carcinoma (ILC) is a special histological subtype accounting for 10–15% of breast cancers. ILC responds poorly to neoadjuvant chemotherapy, but appears to respond well to endocrine therapy. However, it is unclear whether the molecular changes that occur in response to letrozole differ between lobular and ductal carcinomas.

Methods: Pre- and on-treatment (after 2 weeks and 3 months) biopsies were obtained from 14 post-menopausal women with ER+ histologically confirmed ILC who responded to 3 months of neoadjuvant letrozole and were compared with a cohort of 14 infiltrating ductal carcinomas (IDCs) matched on clinicopathological features. Microarray gene expression data were generated. Dynamic clinical response was assessed for each patient using periodic 3D ultrasound measurements performed during treatment. Response was defined as a reduction of >70% in tumour volume by 3 months.

Results: Unsupervised analysis using the 500 most variable genes across samples at pre-treatment was able to distinguish between IDC and ILC with 89% accuracy. Supervised analysis (Rank Products, FDR = 0.01) identified 207 genes differentially expressed: 136 with significantly lower expression and 71 (including e-cadherin) with higher expression in IDC compared with ILC. The 136 genes were functionally enriched for immune and extra-cellular matrix (ECM) remodelling. Differences in gene expression between IDCs and ILCs were maintained during treatment. The most consistently changed genes (n = 377) over 3 months on letrozole from a pairwise analysis in responding IDCs were enriched for down-regulation of proliferation and up-regulation of immune/ECM remodelling genes. This pattern of changed expression was mirrored in the lobulars suggesting a similar molecular response to letrozole.

Conclusions: This is the first study of molecular changes in ILC in response to endocrine therapy to date. The genes which change on letrozole are similar in ILC and IDC. Differences in gene expression can distinguish between patient-matched ILC and IDC at diagnosis and are maintained at each time point on treatment.

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