Emerging Evidence in Breast Cancer

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Breast cancer continues to represent a significant economic and clinical burden to healthcare services worldwide. In Ireland, breast cancer is the most commonly diagnosed female cancer with just over 3,000 cases annually. Of these, approximately 600 cases a year are accounted for by a subgroup of hormone sensitive, Her-2 negative breast cancer that has not spread to the axillary lymph nodes. The treatment landscape for this group of patients has underwent radical change in the last 15 years. While the vast majority of patients with this disease derive most benefit from anti-hormonal therapy, a large proportion would have received adjuvant chemotherapy to reduce the risk of disease relapse by capturing the small number of patients that derive a benefit. This has been particularly relevant in pre- and perimenopausal women. The routine introduction of the 21-gene assay also known as Oncotype Dx has challenged this approach.

The 21-gene test (Oncotype DX, Genomic Health, Inc., Redwood City, CA, USA) is a gene-expression profiling assay validated to predict the estimated rate of distant recurrence of breast cancer and the likelihood of adjuvant chemotherapy benefit in patients with this type of breast cancer. The assay uses reverse transcriptase polymerase chain reaction to quantify the presence of specific mRNA for 16 cancer genes and 5 reference genes in a breast cancer tumour block. These results are then combined into a single recurrence score (RS), expressed on a continuous scale of 0 (low risk of recurrence) to 100 (high risk of recurrence). Following the results of the TAILOR-X trial (Trial Assigning Individualized Options for Treatment), the RS which predicts chemotherapy benefit differs according to patient age. In women older than 50 years, an RS of over 25 may suggest chemotherapy benefit, while in women, aged 50 years and under, with certain high-risk tumour features, chemotherapy may need to be considered with an RS from 16.

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In 2005, when I worked in the National Cancer Institute, Maryland, access to the 21-gene assay was routine for this patient group. Access had permitted a sophisticated discussion regarding the likelihood of patient outcome and the need for chemotherapy. When I moved back to Ireland to start a consultant post in 2006, this was not the case. Personally, it felt like a step back as I was forced to use an educational guess as to the need for chemotherapy or not. Thankfully, in 2008, our Irish patients gained access to the 21-gene assay through the TAILOR-X trial, which was achieved through the close affiliation of our National cancer research group formerly known as ICORG (All Ireland Co-operative Oncology group) with the American research group, East Co-operative Oncology Group (ECOG). Through this trial, nearly 700 Irish women gained access to this gene assay which gave us important information regarding their tumour but also aided the international fight against futile chemotherapy administration. Through participation in this trial, recognition of the importance of this assay was identified by all Irish Oncologists and under an initiative by the Irish Society of Medical Oncology (ISMO) which was led by my colleague Prof. Cathy Kelly in the Mater, access was granted to Irish patients by the National Cancer Control Program in 2011. This was an achievement on two fronts. First, we had gained access in the middle of an economic crisis and second, we were the first European country to gain reimbursement.

Once access was achieved, our intention was always to assess the real-world impact of this assay. We anticipated that not only would this assay save many hundreds of women from the ill-effects of chemotherapy but it would also prove cost effective for the Irish taxpayer. In 2015, Dr Lillian Smyth and I published our primary analysis of the impact of this assay on chemotherapy administration. At that time, we noted a 59% reduction in chemotherapy administration in this patient group. Following the official publication of the TAILOR-X trial in the New England Journal of Medicine, Dr Lynda McSorley and I performed an updated analysis of these results.

This was presented in Chicago at the annual American Society of Clinical Oncology meeting in June 2020. Patients with hormone receptor positive, Her-2 negative breast whose tumour samples were tested with the 21-gene assay between October 2011 and February 2019 were identified retrospectively through electronic records. Patients were identified between October 2011 and February 2013 from eight cancer centres nationally through pathology departments in each hospital. Between February 2013 and February 2019, patients were identified from St Vincent's Healthcare Group via the pathology department. In total, 963 patients who had undergone 21-gene testing with this specific breast cancer subtype were identified. Following international guidelines, 846 of these patients would have been recommended chemotherapy. Using the 21-gene assay, the number recommended chemotherapy fell to 262. This was a massive 69% reduction in chemotherapy administration within this patient group. This also resulted in a net saving to the taxpayer of 1.2 million euros. We estimate that this patient cohort represents about one quarter of the patients that would have been tested in Ireland within this period and therefore the savings could approach 5 million euros.

However, this estimate is extremely conservative as it does not account for the financial impact of absenteeism from work and child care costs while undergoing treatment. Also, while we recognise the financial gain is extremely important as we continue our drive for novel and often expensive drugs for our patients, we cannot underestimate the benefits of chemotherapy avoidance both from a physical and psychological point of view. Chemotherapy avoidance will result in less menopausal symptoms, less infertility, less hair loss, more job security, less cognitive issues, less susceptibility to infection which is particularly pertinent as we navigate the current Covid pandemic. Furthermore, while the majority of patients afflicted by this disease are female, men with breast cancer also benefit from this assay.

The emergence and incorporation of validated multigene diagnostic tests into international cancer management guidelines have resulted in a tailored treatment plan that avoids systemic chemotherapy in large numbers of women with early stage breast cancer. The 21-gene assay is just one example of the emerging technologies towards the goal of precision medicine, a targeted therapy for all. Clinical trial participation is key if we are going to achieve this.