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De-escalating and escalating treatment beyond endocrine therapy in patients with luminal breast cancer

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ABSTRACT

Luminal breast cancers demonstrate significant molecular and clinical heterogeneity, despite the commonality of shared expression of the estrogen receptor (ER). To date, no clinical trial has prospectively investigated the optimal chemotherapy regime according to luminal type, highlighting a paucity of data furthermore required to guide treatment decisions. Current methods of predicting advantage from adjuvant chemotherapy lack refinement and can over-estimate the risk of relapse, inevitably leading to a proportion of patients being unnecessarily exposed to chemotherapy. This paper will explore the evidence behind modalities which may add further value to existing known clinicopathological and molecular profiling techniques in predicting clinical benefit from chemotherapy. Adjuvant chemotherapy regime choice in the context of early luminal breast cancer types will be discussed, and areas for further research and debate identified.

The issue of how best to identify patients who will benefit the most from adjuvant systemic therapy for estrogen receptor (ER) positive early breast cancer remains a conundrum. Adjuvant chemotherapy does not come without a significant price. First, the personal cost to the patient, who is put at risk of serious, potentially life-threatening, toxicities associated with the treatment itself, as well as the additional consequences of lost productivity and possible duress sustained during the (often prolonged) period of treatment and recovery. Second, financially, in the form of the pecuniary cost of the drugs themselves, the fiscal expenditure associated with treatment administration and monitoring, and supportive care required by patients throughout the course of therapy and into long term survivorship. In the setting of disease with a significant likelihood of recurrence, these costs and risks are invariably considered to be outweighed by the potential gain made in terms of disease- and overall survival rates. Conversely, many ER positive early breast cancers have an excellent prognosis, and stand to gain little, if anything, from the addition of adjuvant chemotherapy. Indeed, in these patients, adverse consequence may outweigh any clinical advantage, to potential calamitous effect.

Seminal trials in early breast cancer, involving adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy versus no further treatment have provided long-term survival data in the setting of early disease [1]. After a median follow up of 28.5 years, whilst CMF bestowed a significant overall risk reduction of disease recurrence in node positive patients, 22% of the untreated patient population remained disease free. Patients with ER negative, node negative disease who did not receive adjuvant systemic therapy demonstrated an even higher disease-free survival rate of 40% after 19.2 years of follow up, which suggests loco-regional treatment alone is sufficient to effect long term disease-free status in a significant proportion of patients. Similar observations were made by the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials group in trial B-13, which randomised ER- and node negative patients to surgery plus adjuvant MF chemotherapy, or surgery alone. After sixteen years of follow up, 63% of the surgery monotherapy arm remained free of recurrence, with an overall survival of 65% [2]. Despite these statistics, many

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women are presently still over-treated, notwithstanding evolving knowledge of the clinical and molecular heterogeneity observed in breast cancer. Furthermore, once the decision is made to give chemotherapy, the most appropriate chemotherapy regimen according to intrinsic cancer subtype remains a concept without consensus.

This paper will explore the evidence behind modalities which may add further value to existing known clinicopathological and molecular profiling techniques in predicting clinical benefit from chemotherapy. Adjuvant chemotherapy regime choice in the context of early luminal breast cancer types will be discussed, and areas for further research and debate identified.

At least four intrinsic molecular subtypes of breast cancer have been identified by gene-expression profiling studies [3,4]. Luminal breast cancers, which constitute approximately 60% of all breast cancers, arise from luminal epithelial cells lining the mammary ducts, and demonstrate positive expression of hormonal receptors and other genes involved in ER activation. Luminal A tumours classically exhibit strong expression of ER and progesterone receptor (PgR), a low histological grade and proliferative index, and negative expression of human epidermal growth factor receptor 2 (HER2). In contrast, luminal B subtypes characteristically express pathologically higher tumour grades and Ki67 indices, reflective of a greater proliferative rate. Additionally, they typically display a comparatively weak expression of ER, weak/loss of expression of PgR, and can be either HER2 positive or negative [5]. Perhaps unsurprisingly, a luminal B subtype confers a poorer prognosis than luminal A, although overall, luminal breast cancers are generally associated with a more favourable outlook than their HER2 enriched and ER-negative subtype counterparts [6].

1. Gene signature tests

In the era of personalised medicine, commercially available genomic panel tests have allowed clinicians to characterise tumour gene signatures to form a predictive analysis of clinical outcome [7,8]. Today these predictive models are increasingly utilised in conjunction with clinicopathological prognostic markers, such as patient age, tumour size, grade, nodal status and hormonal and HER2 receptor status, in order to assist clinical decision making. Gene signature tests are particularly influential in guiding treatment recommendations in ER positive, node-negative, HER2 negative cases, wherein the optimal strategy is often unclear [9,10]. Luminal B cancers have predictably high recurrence scores and poor prognostic signatures [11], and as such, coupled with its reputed chemosensitivity, the common practice of offering adjuvant cytotoxic agents to patients with luminal B disease and intermediate-to high-risk clinicopathological features is relatively uncontroversial. In contrast, discriminating between high and low risk luminal A cancers remains a contentious topic, wherein cases of luminal A disease with high clinicopathological or genomic risk factors are often considered for chemotherapy.

Undoubtedly, genomic tools have positively assisted clinical decision making, but there is evidence that genomic assessment may still over-estimate the risk of disease relapse. Retrospective 21 gene assay (Oncotype Dx) analyses of archived tissue obtained in large breast cancer studies have identified a sizeable population of patients who may otherwise have been offered chemotherapy, and consequently over-treated, upon having been deemed at genomic “high risk” of recurrence. In patients enrolled in the NSABP B20 trial, which compared the effect of tamoxifen alone versus tamoxifen plus chemotherapy in ER positive, node negative early breast cancer, 60.5% of those who received tamoxifen alone, who were retrospectively defined as being at high risk of recurrence, remained free of distantly recurrent disease at 10 years [12]. Analogous findings were demonstrated in a node positive population derived from SWOG S8814, a trial that studied the effect of tamoxifen alone versus tamoxifen plus anthracycline-based chemotherapy. In patients with node positive disease who were found to have a high recurrence score, 43% remained event-free at ten years, despite not receiving chemotherapy [13]. The MINDACT trial, which enrolled mainly luminal type cancers, provided the first level IA evidence suggesting it is safe to omit chemotherapy in patients who demonstrate a low 70-gene signature score (MammaPrint) [14]. MINDACT data also elegantly demonstrated that at five years, the majority (90.6%) of patients identified to be at high risk of recurrence according to both clinical and genomic prediction remained free of distant metastases, with a disease free survival rate of 85.3% and overall survival of 94.7%. Undoubtedly, this effect is in part attributable to the adjuvant chemotherapy that this group was universally recommended to receive (3.9% did not receive chemotherapy), Nevertheless, these high rates of survival most likely also reflect the endurance of those patients who were rendered disease-free by surgery alone.

Despite the recent advent of molecular genomic analysis of tumours and ensuing additional enhancement in risk assessment, the ability to identify the subset of early breast cancer patients who harbour micrometastatic disease postoperatively (who would therefore stand to benefit most from systemic adjuvant therapies) continues to be an elusive goal. Tools that may allow clinicians to detect the presence of active micro-metastatic disease may help in refining prognostic assessments.

2. CTCs and ctDNA

Scientific discovery is ongoing into less invasive modalities which may detect malignancy in its early, recurrent and metastatic stages, assess mutational status, as well as predict likelihood of both treatment response and resistance. Peripheral evidence of malignant disease can be assessed in the circulation by way of two sources: circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA), which represents the subset of circulating free DNA that contains the same somatic chromosomal re-arrangements as can be found in the patient's tumour. The comparatively lower tumour burden found in early stage disease correlates with much lower (or absent) concentrations of ctDNA, posing a challenge to investigators – as such, the majority of previous studies have concentrated on metastatic populations. ctDNA has previously been shown to be a sensitive biomarker of metastatic breast cancer, with evidence of correlation between ctDNA levels and treatment response [15]. ctDNA has been detected at high frequencies and levels in patients with metastatic breast cancer, and to a lesser, but still significant, extent in localised disease [16]. In a prospective cohort study of patients receiving neoadjuvant chemotherapy for early breast cancer, mutation tracking in serial plasma samples demonstrated the ability of ctDNA to predict relapse, with a median lead time of 7.9 months over clinically detected relapse [17]. In a small retrospective study of patients with non-metastatic, predominantly node negative, ER positive, HER2 negative breast cancer, elevated plasma ctDNA levels preceded clinical relapse in 86% of patients, with a mean lead time of 11 months. Furthermore, in patients with long-term disease-free survival, ctDNA was undetectable in post operative samples, in contrast with those with established high quantities of ctDNA, which predicted a correlative poor survival [18] (see Table 1).

Detection of CTCs has shown a similar association with poor prognosis in early breast cancer. Prospective collection of peripheral blood samples from chemotherapy-naïve patients with operable Stage I-III breast cancer by one group revealed 24% of those sampled had detectable CTCs, the presence of which predicted a

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