Original article

The continued evidence from overviews: What is the clinical utility?

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ABSTRACT

The Oxford Overview process has provided us with extremely high-powered meta-analyses assessing the role of adjuvant chemotherapy in early breast cancer. From the most recent publication, the proportional benefits from chemotherapy are relatively equivalent across all patient subgroups, a finding contradictory to our growing understanding of the role of tumour biology in dictating chemosensitivity. Several factors, including heterogeneity of patient groups and chemotherapy regimens, lack of data on underling tumour biological subtypes, and confounding effect of chemotherapy-induced ovarian suppression in premenopausal women with hormone receptor positive breast cancer, impact on the applicability and clinical utility of the Overview in current and future oncological practice. With these considerations, the Overview has become less clinically relevant as a tool for guiding adjuvant chemotherapy treatment decisions, and a new direction is required.

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Introduction

The Oxford Overview began in 1985, aiming to amalgamate and consolidate data from all patients participating in adjuvant therapy breast cancer trials. Results from meta-analyses of adjuvant chemotherapy trials were first published in 2005 [1], and were most recently updated in 2012, where, in addition to the comparisons of the previous publication, the effect of taxanes was examined, as was the impact of chemotherapy dose [2].

Findings from the Oxford Overview 2012

Incorporating individual patient data from 100,000 women from 123 adjuvant trials, these analyses are an impressive undertaking, and achieve a power such as not possible in individual adjuvant trials. Combined analyses of taxane-based trials encompassing 44,000 women demonstrated that the addition of taxanes to standard (predominantly anthracycline-based) chemotherapy reduced relative risk of recurrence by 14%, \( p < 0.00001 \), breast cancer specific mortality by 13%, \( p < 0.00001 \), and all cause mortality by 11%, \( p < 0.00001 \) [2]. Due to heterogeneity of treatment regimens, analyses were also performed based on the amount of non-taxane chemotherapy used. The addition of taxanes significantly improved outcomes when the amount of non-taxane chemotherapy was equivalent or increased by less than double between treatment arms [2]. Interestingly, when the addition of taxanes was roughly counterbalanced by doubling the number of non-taxane-based chemotherapy, no statistically significant advantage from taxanes for relapse (RR = 0.96, \( p > 0.1 \)), breast cancer mortality (RR = 0.94, \( p = 0.33 \)), or overall mortality (RR = 0.96, \( p > 0.1 \)) was evident. Anthracycline-based chemotherapy was also compared with cyclophosphamide/methotrexate/fluorouracil (CMF) chemotherapy, with four cycles of doxorubicin/cyclophosphamide (AC) found to be relatively equivalent to standard CMF, while outcomes were improved when higher cumulative doses of anthracyclines were used [2]. Finally, analyses from 64 trials with very long-term follow up, comparing either anthracycline-based chemotherapy or CMF with no chemotherapy, demonstrated a significant benefit from chemotherapy, with a 22% to 36% proportional reduction in breast cancer mortality. Both disease free survival and overall survival were also improved to a similar extent in those patients who received chemotherapy [2].

In addition to these results, perhaps the most striking finding of these latest Oxford Overview meta-analyses was that all patients, regardless of tumour stage, nodal status, oestrogen receptor (ER) status, or age appeared to have a relatively equal proportional benefit from the addition of chemotherapy [2]. This is a particularly interesting result that flies in the face of the concept that tumour biology is associated with differential chemosensitivity.

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All breast cancers are equal, but some are more equal than others

There is increasing acknowledgement that breast tumour biology may influence both prognosis and response to chemotherapy [3]. In particular, a subset of ER positive (ER⁺) breast cancers seem not to benefit from adjuvant chemotherapy, being relatively chemoresistant and having an otherwise excellent prognosis with endocrine therapy alone [4–9]. Through the utilisation of genomic assays, we are now able to stratify ER⁺ breast cancers into higher and lower risk disease. The 21-gene recurrence score (RS), now marketed as Oncotype DX (S9), has been retrospectively validated as a risk prediction tool in ER⁺ node-negative early breast cancer (EBC) treated with tamoxifen [6], ER⁺ node-negative EBC treated with adjuvant cyclophosphamide/methotrexate/fluorouracil (CMF) [7], ER⁺ node-positive EBC treated with cyclophosphamide/doxorubicin/fluorouracil (CAF) [8], and ER⁺ node-positive or node-negative EBC in postmenopausal women treated with either tamoxifen or aromatase inhibition [9]. Other gene signatures, such as the 70-gene signature [10] (MammaPrint™), PAM50, and Gene expression Grade Index (GGI) [11], have been defined, each one distinguishing different breast cancer subtypes, and allowing a more accurate relapse risk assessment than standard clinico-pathological characteristics alone. Furthermore, genomics has demonstrated that breast cancers of different molecular subtype respond differently to chemotherapy. In particular, patients with luminal A-like breast cancer derive minimal benefit from chemotherapy and therefore in some of these patients chemotherapy might be avoided. Contrarily, the Oxford Overview results fail to demonstrate any differential chemotherapy response within luminal (ER⁺) breast cancers, with all patients, regardless of ER status, or indeed any characteristic, receiving the same proportional benefit from chemotherapy.

Issues with the Overview

Assessment of tumour biology

Characterisation of breast cancers into various subtypes is becoming essential to accurately stratify need for chemotherapy. The Oxford Overview collaborators have made valiant attempts to include more subgroups in their analyses; however critical information that may have allowed accurate separation of luminal A from luminal B tumours was never collected in the original trials. There is no genomic data available to allow categorisation of breast cancers into molecular subtypes, nor is there data that would allow immunohistochemical (IHC) classification to be implemented as a surrogate method of subtype determination. Luminal breast cancers may be categorised with IHC expression of ER, progesterone receptor, HER2, and the proliferation marker Ki67, using a putative cut-off of 14% for the latter to differentiate low-proliferating luminal A from high proliferating luminal B tumours [12,13]. While this approach does require further validation, it has demonstrated reasonable accuracy, with sensitivity and specificity of 72% and 77%, respectively [12]. Unfortunately, though, no data on Ki67 was included in the Oxford Overview analyses, preventing reliable discrimination between luminal A and luminal B tumours, and thus failing to demonstrate that luminal A tumours do not receive significant benefit from chemotherapy. Of note, subgroup analyses of ER⁺ tumours into well/moderately/poorly differentiated tumours have been reported [2], however tumour differentiation is associated with wide inter-observer variability, and is not the most appropriate method for distinguishing between luminal A and B subtypes.

Ovarian suppressive effects of chemotherapy

Retrospective analyses performed on older adjuvant studies (when tamoxifen use was not routine) indicate that there is a survival benefit from chemotherapy-induced amenorrhoea in ER⁺ but not ER⁻ breast cancer [14–16]. This differential effect of chemotherapy by ER status supports the concept that chemotherapy-induced ovarian suppression exerts endocrine effects on ER⁺ breast cancer, and that this might account for the observed efficacy of chemotherapy in premenopausal women. From the Overview meta-analyses comparing CMF with no chemotherapy, breast cancer mortality was proportionally reduced by 43% with the addition of chemotherapy in premenopausal patients with ER⁺ breast cancer (those aged <55 years), compared with 10% for postmenopausal patients (aged 55–69) [2]. This suggests that the benefit from chemotherapy in premenopausal women may have been at least partially due to chemotherapy-induced ovarian suppression, rather than the cytotoxic activity of the agents. Of note, from trials testing polychemotherapy vs. no chemotherapy in premenopausal patients with ER⁺ tumours, the vast majority of patients in the control group did not receive endocrine therapy. Thus the impact of ‘endocrine effects’ induced by chemotherapy would be proportionally greater than that seen today, with endocrine therapy now being standard. In the analysis of polychemotherapy (either anthracycline-based or CMF regimens) vs. no chemotherapy, proportional breast cancer mortality risk in ER⁺ disease was reduced by 28% and 22% for women aged <55 and 55–69 years, respectively [2], i.e. there is a less evident difference between pre- and postmenopausal women in this case. As the chemotherapy regimens included in the combined ‘polychemotherapy’ analysis were heterogeneous, their relative gonadotoxicity is uncertain, suggesting a possible explanation as to why premenopausal patients had a greater benefit with use of CMF alone: alkylating agents, such as cyclophosphamide, are highly gonadotoxic, while anthracyclines are relatively less so. However, as no data are available on rates of chemotherapy-induced amenorrhoea specifically, this remains supposition only. Nonetheless, results reported for the population of ER⁺ patients aged <55 years may, to an extent, be attributable to chemotherapy-induced endocrine effects, and thus overestimating benefits of chemotherapy in this specific population.

Interestingly, in a recent study from Bailey et al. a set of commonly expressed genes between wild-type p53 and ER was demonstrated, with ER being an important inhibitor of wild-type p53 function. Complete inhibition of ER with fulvestrant allowed increased p53-mediated cell death, while tamoxifen, a partial ER agonist, decreased apoptosis [17]. These data provide a potential explanation for resistance of some ER⁺, p53-wild-type breast cancers, and suggest that efficacy of chemotherapy might be increased by combining with complete ER antagonists, rather than partial agonists. Although the effect of chemotherapy-induced ovarian suppression on p53-mediated apoptosis is not yet known, these findings highlight a further confounding factor in the interpretation of the Oxford Overview results relating to the impact of chemotherapy in premenopausal women with ER⁺ breast cancer.

Patient population

In the analyses of polychemotherapy compared with no chemotherapy, the Oxford Overview graphically demonstrates a striking absolute reduction in 10-year breast cancer mortality risk of 6.5%, and absolute reduction in recurrence of 8.0% at 10 years. Absolute benefits in terms of relapse risk for anthracycline-based compared with CMF chemotherapy, and taxane vs. non-taxane chemotherapy are 2.6% at 10 years and 4.6% at 8 years,
respectively. These absolute differences are impressive, however it is important to note that, from the 100,000 women included in the trials from the Oxford Overview, the majority were node-positive (70% across all studies for patients with known nodal status), a patient population where absolute benefits are increased. Comparatively, node-negative disease now comprises over 60% of breast cancer diagnoses, with only one third being node-positive [18]. Furthermore, screen-detected breast cancers, which tend to be smaller, low-risk (luminal A) subtypes [19], have increased in incidence [20]. Thus, the degree to which chemotherapy may have benefitted women in the Overview trials will generally not be replicated in breast cancer patients today.

**Heterogeneity**

The primary objective of the Overview is to pool data from a large number of adjuvant trials to provide high-powered meta-analyses assessing the utility of chemotherapy. Yet while study power is increased dramatically, the pooling heterogeneous groups of patients and heterogeneous regimens can confound results. Fundamentally also, pooling of data across widely variable patient groups to assess one endpoint is contrary to paradigm of tailoring therapy for individual patients.

**Future considerations**

How should treatment decisions regarding adjuvant chemotherapy be made? Utilising results from the Oxford Overview, that all patients stand gain equal proportional benefit, the only relevant factor would be tumour stage. Yet we have already moved beyond this relatively simplistic approach, routinely incorporating tumour biology into treatment decisions [6–11]. In addition to ongoing research into the biological characteristics of different breast cancer subtypes, further refinement of risk prediction models might be achieved through incorporation peripheral factors, including assessment of the host response to the tumour, and markers of micrometastatic disease.

**Immunological host response**

The type of immune response elicited by the presence of a cancer can dictate likelihood of tumour eradication, or conversely progression. Immune responses characteristic of acute inflammation, with induction of CD8+ cytotoxic T lymphocytes, typically lead to tumour rejection, while CD4+ T2 helper cell, T regulatory cell and B cell activation, or immune system activation consistent with chronic inflammation, can promote tumour progression [21,22]. Immune host/tumour interactions may also be important in predicting chemotherapy response. In a study which assessed 17 different gene signatures and their ability to predict response to neoadjuvant anthracycline +/- taxane chemotherapy, high immune module scores/expression correlated with increased rates of pathological complete response in all breast cancer subtypes (luminal A and B, HER2 positive and triple negative) when defined by IHC [23]. Ongoing research in this field may help to elucidate why chronic compared with acute immune responses are elicited in certain individuals, as well as immunotherapeutic interventions that might promote tumour rejection.

**Markers of micrometastatic disease**

Tumour staging and genomic analyses aim to provide a reasonable estimate of likelihood of the presence of micrometastases, but do not measure these directly. Indeed, to date, there are no tools in routine clinical practice, which can accurately identify patients with micrometastases. However, newer techniques, which remain in experimental development, are promising, whereby micrometastases may be detected through analysis of disseminated tumour cells (DTC), circulating tumour cells (CTC), cell-free DNA (cf-DNA) plasma microRNAs, or metabolomics.

DTC can be detected in bone marrow using highly sensitive and specific methods. Similarly, improved CTC extraction methods can allow isolation of single CTC amongst a background of several million cells [24]. Several studies have now demonstrated the prognostic impact of detecting DTC or CTC in EBC patients [25–30]. In a pooled analysis, which included over 4700 breast cancer patients, significantly decreased overall survival was seen in the 30% of patients with DTC in bone marrow, including some patients with small node-negative tumours, when compared to patients without DTC [25]. Persisting DTC in bone marrow after completion of adjuvant therapy may also predict disease recurrence [26,27]. Detection of CTC in EBC patients has been shown to predict poor survival in both the neoadjuvant [28] and adjuvant [29,30] settings, while EBC relapse has been associated with concentration of cf-DNA [31] and miRNA [32]. Another emerging method for detecting residual microscopic disease following primary breast cancer surgery is metabolomics, the study of the metabolites, or end products, derived from complex physiological and pathological processes. Malignant transformation is accompanied by a considerable metabolic shift, which can result in a markedly different metabolic landscape between cancer cells and normal cells, and between cancer patients and healthy matched controls [33]. In a previous study by our group, comparison of metabolomic spectra from early and advanced breast cancer patients allowed discrimination between these two patient groups with an accuracy of 83.7%. Furthermore, patients with EBC with metastatic disease-like metabolomic spectra had increased chance of relapse (unpublished data).

Ultimately each of these techniques requires further validation before entering standard clinical practice; however their development represents an exciting step forward in the holistic approach to relapse risk prediction.

**Conclusions**

Ideally, in coming years, assessment of the utility of adjuvant chemotherapy in an individual patient will be based on a combination of tumour biological characteristics, host characteristics, and presence or absence of markers of micrometastatic disease. As the Oxford Overview contains limited, if any, information relating to each of these specific factors, it will become increasingly difficult to incorporate the Overview data into future adjuvant chemotherapy decisions. Certainly, information gained from the Overview has been useful up until current times, and the efforts of the Overview committee laudable. Yet as we move towards personalised oncological practice, the clinically relevance of Oxford Overview lessens with each passing year.

**Conflict of interest statement**

No conflict of interest to declare.

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