Fighting overtreatment in adjuvant breast cancer therapy

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In *The Lancet* today, Kathy Albain and colleagues present 10-year results of the SWOG-8814 (INT-0100) trial,[1] which since its first presentation has defined a standard of care in breast cancer—ie, adjuvant cytotoxic chemotherapy is beneficial for node-positive patients. However, use of nodal status as the main prognostic factor leads to huge overtreatment for many patients. Even in today's paper, the absolute 10-year overall survival difference was just 5%, more than enough to justify a desired standard of care nowadays but, ultimately, leaving 95% of patients with many side-effects.

Albain and colleagues have shown that addition of tamoxifen to cyclophosphamide, doxorubicin, and fluorouracil (CAF) within the first 6 months exerts a longlasting effect. In terms of tumour biology, this outcome is exciting and surprising from a theoretical point of view. Whereas outcome curves for endocrine-responsive breast cancer mimic those for chronic diseases (ie, show an almost linear long-term event pattern),[2] addition of CAF seems to widen the survival curve difference up to about year 5 after surgery.

What is the underlying biology? Are dormant micrometastases eradicated successfully during those 4–6 months of chemotherapy, reducing the number of later relapses permanently? Treatments that change the microenvironment where these dormant cells supposedly survive have gained attention in the adjuvant setting.[3] Early cytotoxic therapy could target macrophages and affect the patient's immune response, thereby contributing to a so-called carryover effect of CAF in the first 5 years.

A different observation can be made for the comparison of CAF and concurrent tamoxifen with CAF followed by tamoxifen. Current standard practice is to avoid concomitant tamoxifen and chemotherapy based on previous findings of SWOG-8814 and due to concerns about preclinical antagonism, despite some controversial reports.[4] In today's report, the outcome difference between concurrent and consecutive tamoxifen arose late in the survival curves, provoking speculation about a sustained early effect on the tumour microenvironment. These findings lend support to a hypothesis about the importance of indirect effects of adjuvant therapy, which could act in a direct, toxic, tumour-cell-eliminating manner to a lesser extent than we used to think.[5]

CAF, while statistically beneficial for the cohort studied, is not without substantial early and late toxic effects, including early deaths, later congestive heart failure, and secondary neoplasms. Thus long-term follow-up is very important in such trials but is increasingly difficult to find funding for, particularly in industry-sponsored studies. The ultimate risk–benefit assessment will need more than just achievement of the first significant p value, which nowadays seems to be good enough for major publication and even for regulatory approval of a new therapeutic intervention.

There is a price to pay for a 5% overall survival benefit and, for that reason, identification of subgroups of patients who have an above-average outcome is important. Unplanned subgroup analyses by Albain and colleagues suggest patients at high risk of relapse (large tumours, age <65 years, ≥4 affected nodes) mainly show a benefit of adjuvant therapy. Conversely, patients at low risk of relapse (breast conservation, age ≥65 years, 1–3 affected nodes) might show a marginal or no benefit from CAF.

Since risk is something we cannot change, response prediction is nowadays judged more important for clinical decision making than risk itself,[6] but calculation of individual benefit is still poor. Avoidance of unnecessary or ineffective treatment should be one

of the main goals in adjuvant breast oncology today. Unfortunately, both patients and doctors hunt for tiny statistical differences in survival curves. As outlined elegantly by Dodwell and colleagues,[7] this search could not only lead to an oncological approach of unlimited addition that we will not be able to afford, but would also end inevitably in indeterminate polypharmacy with substantial risks of unexpected toxic effects eating away whatever progress we might make.

In SWOG-8814 and other adjuvant trials, overall benefit is mainly accounted for by the high-risk subgroup of patients. This observation is substantiated by findings of another SWOG-8814 publication by Kathy Albain and co-workers in *The Lancet Oncology* today,[8] in which a correlation between the 21-gene recurrence score and CAF benefit is described. On the basis of 367 patients from SWOG-8814 for whom tumour RNA was available, the overall CAF benefit described in today's paper in *The Lancet* was present exclusively in the highest risk subgroup (recurrence score ≥31),[8] which comprises not even a third of the overall trial cohort.

Does the 21-gene assay truly provide a biological approach to risk assessment and response prediction compared with classic immunohistochemical measures? This question is currently under investigation in large prospective clinical trials, but similar data have been reported for other multigenomic assays.[9] Findings of the molecular analysis presented in *The Lancet Oncology* accord with those of the subgroup analysis in *The Lancet*—that patients at low risk of relapse might not benefit at all from adjuvant chemotherapy. If this result is true, overtreatment could be even more striking in patients with node-negative breast cancer.

"First, do not harm" remains the main principle in medicine. To be able to follow this rule, we need to better understand the biology of breast cancer. The mistake of "one treatment fits all" can only be ameliorated when we critically review trial designs of adjuvant breast oncology. Selection of precisely defined cohorts for phase 3 trials is necessary, despite pressure to the contrary by scientific ambition, pragmatism, and demands of industry.

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