E13. State of the art of adjuvant therapy

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In 1997 the results of study NSABP B20 showed that adjuvant chemotherapy was also associated with benefit in women with axillary lymph node-negative, oestrogen receptor-positive breast cancer.[1] The results of that study for oestrogen-receptor positive tumours implied that chemotherapy was universally useful and that, in the light of other studies,[2,3] such a systemic therapy found indication irrespective of tumour size, oestrogen receptor status and axillary lymph node involvement. The results of NSABP B20 and their interpretation corresponded to the peak of the era of 'one size fits all'. In a way it also marked the beginning of the end of that era and the shift to the ongoing phase of treatment tailoring and individual assessment of risk and therapeutic indication. It is almost symbolic that the same NSABP B20 trial was the source of the data to show that, based on their tumours' characteristics, different risks can be assigned to individual patients selected according to the same criteria within the trial, and that the different individual risk was associated with either no benefit or major benefit from systemic chemotherapy added to tamoxifen.[4]

With the above introduction in mind it is easy to understand that the current state-of-the-art of adjuvant systemic therapy of breast cancer reflects the merging of different lines of research that provide the basis for treatment selection with chemotherapy, hormonal therapy and targeted drugs in combination, in sequence or alternatively. A reference to some relevant aspects related to chemotherapy, HER2-directed treatment and new progrnostic/predictive classifiers will be the subject of this short review.

The most relevant acquisitions contributing to the current use of adjuvant chemotherapy are the established role of the taxanes, paclitaxel and docetaxel, and the evidence supporting the clinical relevance that different sequencing of non cross-resistant regimens have. G. Bonadonna and his collaborators pioneered the latter approach with trials assessing the different benefit associated with different sequences of doxorubicin (A) and cyclophosphamide, methotrexate, and fluorouracil (CMF) in operable breast cancer.[3,6–8] Only recently has the work of the NEAT and SCTBG investigators showed that epirubicin before CMF is significantly more effective than CMF given for the same total duration of treatment.[9] Although inherently evident from the studies of Bonadonna (BMJ), the hypothesis had not been documented until the report of the investigators from the UK.[9]

It is not surprising that the merits of sequential chemotherapy are also present with regimens adopting the taxanes. The standard use of AC followed by paclitaxel common in North America is based on the CALGB 9344 study that used AC for four cycles as the conventional therapy in the comparator arm.[10] The study design left unclear the point whether the improved efficacy observed with addition of paclitaxel was due to the sequential administration of non cross-resistant drugs or to the more prolonged duration of the taxane-containing therapy. The French study PACS-01 showed that the sequence of three cycles of fluorouracil, epirubicin and cyclophosphamide (FEC) followed by three cycles of docetaxel provided significantly better disease free survival than six cycles of FEC.[11] The identical number of cycles of both regimes in the PACS 01 study ruled out that duration was responsible for the measured advantage.[11] The sizeable benefit provided by the sequential administration of chemotherapy regimens containing taxanes is confirmed by two other studies. In the European Cooperative Trial in Operable breast cancer (ECTO) the sequence of doxorubicin and paclitaxel followed by CMF afforded significantly longer DFS than the sequence of doxorubicin and CMF pioneered by G. Bonadonna.[8,12,13] The results of the Breast International Group 02–98 randomised trial go in the same direction and show a small but relevant advantage of the sequential use of doxorubicin followed by docetaxel followed by CMF than concurrent docetaxel and doxorubicin followed CMF, or the more 'Bonadonna-like' regimen of four cycles of doxorubicin followed by three cycles of CMF.[14] The data of the latter two studies are especially relevant in indicating that use of taxanes as well as scheduling is important in gaining the best results in high risk operable breast cancer. Together with the data of the PACS01 study, the ECTO and the BIG 02–98 trials contribute to define anthracycline- and taxane- containing regimens as reference adjuvant treatment for early breast cancer. The undisputed role of taxanes finds additional support in the Breast Cancer International Research Group 0001 study that compared six cycles of fluorouracil, doxorubicin and cyclophosphamide (FAC) with six cycles of docetaxel, doxorubicin and cyclophosphamide (TAC)

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in node positive operable breast cancer.[15] Whether docetaxel should be administered as in the TAC regimen or in the PACS01 or the BIG 02–98 trials cannot be concluded from the available studies. It should however be noted that sequential regimens always proved superior to the non sequential ones whenever a formal test was conducted.

The successful and rapid development of HER2-directed adjuvant systemic therapy with trastuzumab for women with HER2-overexpressing tumours is one of the most impressive results in the history of adjuvant systemic treatment of breast cancer that also sets the stage for the beginning of the era of targeted therapies. The results of five studies showed beyond doubt that the addition of trastuzumab to chemotherapy or the use of the antibody after chemotherapy is an improvement in the management of early breast cancer and an outstanding opportunity for women with HER2 expressing tumours.[16–19] The extent of the benefit and the excellent tolerability profile of the monoclonal antibody have obtained that the National Comprehensive Cancer Network (NCCN) Guidelines very rapidly adopted the recommendation that adjuvant trastuzumab therapy should be administered as a standard treatment in patients with node negative high risk or node positive early breast cancer 'positive' for HER2 as defined based on immunohistochemistry (IHC) or fluorescence *in situ* hybridisation (FISH).[20] Trastuzumab is now approved worldwide as adjuvant treatment in HER2 positive early breast cancer patients, although approval is different in different regions of the world as a reflection of the different design of the studies submitted for approval (weekly during taxanes as in the NSABP B31 trial (the FDA), and three-weekly after all chemotherapy and radiotherapy as in the HERA trial (the EMEA)), and entered the era of being state-of-the-art therapy in this setting of disease at the cost of an acceptable tolerability. The results of the available studies so far show that trastuzumab is effective in all subgroups of women enrolled into the different trials.[16,17,19] The key questions being addressed at this stage are related to the optimal duration of treatment with approaches that are split between waiting for the results of the 2-year long therapy arm of the HERA trial[17] and conducting studies replicating the short 9-week long duration of trastuzumab therapy explored in the FinHER study.[19] Another point that is still unsettled concerns the optimal timing of adjuvant trastuzumab therapy and the opportunity of co-administering chemotherapy as in all trials but the HERA, an aspect that will be clarified by the ongoing follow-up of the NCCTG trial that had a comparison of control therapy with one arm in which trastuzumab started concomitantly with weekly paclitaxel and another arm in which trastuzumab started, as in the HERA, at the end of all chemotherapy.[16] A final and critical question being addressed is the definition of the tumour's characteristics associated with likelihood of resistance to trastuzumab. The latter aspect is key and in line with the ongoing effort of tailoring treatment to the individual needs of the patients and the characteristics of the disease. The topic is probably the most relevant to the daily application of adjuvant systemic therapy.

The application and refinement of adjuvant chemotherapy over the years has significantly improved the disease free and overall survival in patients with operable breast cancer.[21] As cited at the beginning of this article, there is growing awareness that the empirical approach that culminated in the original presentation of the NSABP B20 study has the inherent limitation of delivering the same therapy to all patients, including those who are potentially cured by locoregional modality and those who have residual tumour resistant to the prescribed therapy. The result of such an empirical 'one-fits-all' approach is therefore that of exposing many patients to ineffective therapies and unnecessary toxicity while wasting economical resources. This scenario underscores the need for designing treatments tailored to the characteristics of the primary tumour and to the clinical needs of the individual patient.

Several guidelines have been developed to assist cliniciansin selecting adjuvant therapy for women with operable breast cancer.[22,23] The final recommendation for some subgroups of patients differs between guidelines underscoring the challenge of consistently defining the actual risk and indication based on the currently selected variables, including TNM characteristics and limited tumour biology.

High-throughput technologies, like gene expression profiling, gene variants, and epigenomics allow for probing and categorising of the biology of the tumour and the patient characteristics at a much higher level of complexity. It is reasonable to expect that a combination of several molecular biomarkers selected from thousands of candidate biomarkers could predict prognosis and patterns of response to therapy of individual patients better than a single or few biomarkers. These technologies are providing new venues to class prediction where the class can either be risk or probability of benefit. To be useful, the application of a genomic classifier should result in better outcome or similar outcome with fewer adverse events and less expensive treatment than in the patients in whom the classifier was not applied.[24]

Multi-gene expression classifiers have their main field of application in the *a priori* identification of the type of adjuvant treatment that is actually needed in individual cases. A number of classifiers are currently available for research as well as for commercial use, and all of them define a new modality and opportunity for decision-making in oncology.[4,25–27] Their impact

in improving the application of adjuvant therapies to individuals is being tested in two major randomised trials in node-negative and conventionally 'low risk' patients, the MINDACT [28] and the TAILORx trials. [29] While those trials will be conclusive in defining whether such approaches deserve to enter the level of state-of-the-art, the latest version of the NCCN guidelines has just included the 21-gene Recurrence Score assay in the work-up of women with hormone receptor positive, HER2-negative disease [30] as complementary evidence capable of refining the individual indication to hormonal therapy only or to the sequence of chemotherapy and hormonal treatment.

Conflict of interest statement

Author has had the role of Advisor for all of the following entities: Roche; Genentech; Pfizer; GSK; Lilly; Sanofi-Aventis.

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