Hormone-receptor positive early breast cancer: controversies in the use of adjuvant chemotherapy

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Abstract

Current adjuvant treatments for operable breast cancer include chemotherapy, endocrine therapy in hormone-receptor positive tumors, and trastuzumab for HER2-positive tumors. Metanalyses of randomized trials show that in patients with hormone receptor positive breast cancer the effects of endocrine therapy and chemotherapy on survival are non-mutually exclusive. Most of these patients are therefore considered candidates to combined treatment. Recently, however, the endocrine-responsiveness of tumors has been redefined on clinical, histopathological and molecular bases. An emerging concept is that as endocrine-responsiveness increases, chemoresponsiveness decreases. In the adjuvant setting therapeutic choices are often based on small projected improvements clinical outcomes. As a consequence, the role of chemotherapy and traditional management algorithms in patients with hormone-receptor positive are being challenged. This review will address the current controversy regarding the role of adjuvant chemotherapy, including the newer anthracycline and taxanes-based programs, in these patients.
**Introduction**

Hormone-receptor positive breast cancer, currently defined on the basis of the immunohistochemical expression of the estrogen (ER) and of the progesterone receptor (PgR), constitutes about 60% of breast cancers arising in pre-menopausal women and 80% of those diagnosed after menopause (Clark et al. 1984). Hormone-receptor expression, measured in terms of percentage of positive cancer cells, is a strong predictor of response to endocrine manipulation both in the metastatic and in the adjuvant setting. More recently, hormone-receptor expression has also gained acceptance as a prognostic factor (Goldhirsch et al. 2007).

Multigene expression analysis approaches are providing deeper insights into the biological heterogeneity of breast cancer (Perou et al. 2000). In particular, hormone-receptor positive tumors, which constitute the prevalent phenotype of breast cancer, can be further subdivided into groups according to peculiar gene expression profiles, different clinical behavior and response to anticancer treatments (Sorlie et al. 2001). This growing body of information will hopefully result in accurate tools to tailor treatments on single patients. This approach is profoundly different from the current one, which consists of assigning treatments on the basis of average expected effects in broad categories of patients. Overcoming the limitations of the current approach is warranted in a disease where we tend to treat many patients for the benefit of a few. The area where the debate on treatment tailoring is particularly active is the management of hormone-positive breast cancer, where endocrine therapy is the mainstay of adjuvant therapy (ATAC trialists 2008; Boccardo et al. 2005; Coombes et al. 2007; Cuzick et al. 2007; Early Breast Cancer Trialists' Collaborative Group 2005; Goss et al. 2005; Jakesz et al. 2007; Jonat et al. 2006; Thurlimann et al. 2005). Over the last few years the added benefits of chemotherapy in
these patients have been questioned and its role has undergone a process of critical revision.

**Progress in adjuvant chemotherapy of breast cancer over the last 30 years**

Adjuvant chemotherapy for breast cancer has undergone an evolution over three decades which, with the risk of excessive simplification, may be summarized by defining 3 eras: the CMF (cyclophosphamide, methotrexate and 5-fluorouracil) era, the era of anthracyclines and the current one, which is characterized by the introduction of taxanes. From CMF onward, each significant achievement has been obtained through an incrementalistic strategy based on the availability of newer classes of drugs showing activity in metastatic breast cancer. The average 10-year survival benefit of anthracycline-containing regimens over CMF is estimated to be 4.3% and has been established quite recently by the early breast cancer trialists collaborative group (EBCTG) metaanalysis, which included 14,000 women enrolled in several clinical trials, a number of which was characterized by small sample size and heterogeneous regimens (Peto 2007). The relatively limited increase in the average efficacy, together with the increased burden of toxicity with anthracycline, has fuelled a debate that, despite the metanalysis data, still divides oncologist. Retrospective analyses of the most influential clinical trials have generate interesting hypotheses on the fact that anthracycline-related benefit may be confined to particular subgroups of patients, like those whose tumor carries alterations of HER2 or of DNA topoisomerase IIA (TOP2A), which is one of the pharmacological targets of anthracyclines (Di Leo & Isola 2003; Gennari et al. 2008; O'Malley et al. 2009; Pritchard et al. 2006). At the same time, as already described, the metanalysis suggests that the benefit related to anthracycline tends to diminishes with age resulting in an arguable therapeutic index in older patients.
The story of the incorporation of taxanes in adjuvant chemotherapy regimens is more recent. The results of first-generation studies, aimed at evaluating the worth of adding taxanes to anthracycline in women with higher-risk breast cancer patients (involved axillary lymphnodes), were made public by the end of the ‘90s.

The first two fully published studies dealing with the role of taxanes in women with lymph-node positive disease were the Cancer and Leukemia Group B (CALGB) 9344 (3121 women) and the National Adjuvant Breast and Bowel Project (NSABP)-B28 (3060 women) trials (Henderson et al. 2003; Mamounas et al. 2005). Conceptually, the two studies could be considered similar, comparing chemotherapy with AC vs the same chemotherapy plus 4 cycles of paclitaxel every 3 weeks. In both studies, 66% of the enrolled women had hormone-receptor positive tumors. In the CALGB 9344 study, Tamoxifen was started at the end of chemotherapy in hormone-receptor positive patients. In the NSABP B-28 study, tamoxifen was recommended to women with hormone-receptor positive tumor and to those older than 50 years regardless of hormone-receptor status and was started with the first cycle of chemotherapy. Both studies confirmed the superiority of the taxane-containing arm in terms of disease-free survival, with a proportional reduction in the risk of relapse of 17% (Hazard Ratio-HR 0.83). Differently from the NSABP study, the CALGB 9344 showed also a significant effect on overall survival, with a proportional reduction in the risk of death of 16% (HR 0.84) favoring the experimental arm. Debate around the benefit of adding paclitaxel to anthracycline arose from the report that, in both studies, patients with hormone-receptor positive breast cancer achieved a much more limited and non significant benefit in terms of reduction of the risk of relapse (9% and 10% in the CALGB and NSABP study, respectively). Although a formal test of interaction between treatment arms and hormone-receptor status was not significant in the NSABP B-28 study, these results raised concerns about the worth of adding paclitaxel to AC in patients with hormone-receptor positive tumors.
The Breast Cancer International Research Group (BCIRG) conducted the 001 randomized study, which compared 6 cycles of FAC with 6 cycles of the same regimen but with the substitution of 5-fluorouracil with docetaxel (Martin et al. 2005). The study enrolled 1491 women with lymphnode positive disease and had a “balanced” design, because number of administration and overall duration of treatment were identical in the two arms. The conventional comparator was perhaps more convincing than the 4 cycles of AC of the CALGB and the NSABP studies, because of longer duration and a slightly higher cumulative dose of doxorubicin. Results favored the experimental docetaxel-containing arm, which achieved a significant proportional reduction in the risk of relapse and death of 28% and 30%, respectively. These proportional reductions translated into an absolute gain in 5-year disease free and overall survival of 7% and 6%, respectively. Furthermore, the size of the proportional reduction in the risk of relapse was almost similar in subgroups defined on the basis of hormone-receptor status, as was in subgroups defined on the basis of HER2 status. The introduction of docetaxel increased the global burden of chemotherapy-related toxicity, but no fatal toxic events were registered in the experimental arm of this trial. Subsequently, a study conducted in France (PACS 01) compared, in 1999 women with lymphnode positive operable breast cancer, 6 cycles of FEC with a sequence of 3 cycles of FEC (same as above) followed by 3 cycles of docetaxel administered at 100 mg/m² every 3 weeks (Roche et al. 2006). The experimental treatment was associated with a significant proportional reduction in the risk of recurrence and death of 18% and 27%, respectively. These improvements translated into a 5-year absolute gain in recurrence-free and overall survival of 5.3% and 4%, respectively. Furthermore, halving the total cumulative dose of epirubicin resulted in less cardiotoxic events in patients in the experimental arm. Similarly to the BCIRG 001, also in the PACS 01 the docetaxel-containing arm was superior to FEC in both hormone-receptor positive and negative patients.
Several other first-generation studies have addressed the role of taxanes and their results have been included in metanalyses. At the 31st San Antonio Breast Cancer Symposium sir Richard Peto presented results of the last metanalysis of the EBCTCG (Peto 2007) showing that regimens including these drugs, compared with taxane-free regimens, were associated with a proportional reduction of the yearly risk of relapse and death of 17% (HR 0.83, 2p<0.00001) and 14% (HR 0.86, 2p<0.00001), respectively. Furthermore, results of 13 first-generation studies with taxanes have been the subject of a “pooled data metanalysis” by De Laurentiis et al. and published in the Journal of Clinical Oncology.(De Laurentiis et al. 2008) Despite different methodology, this metanalysis showed similar effects than those reported by Peto, with a proportional reduction in the risk of relapse and death of 22% and 17%, respectively. These benefits are unlikely to significantly affected by the results of a recently published large trial (Taxotere as adjuvant trial-TACT) failing to show benefit of a sequential FEC and docetaxel treatment compared with FEC or a sequence of epirubicin and CMF (Ellis et al. 2009). The overall achievements in the field of adjuvant chemotherapy through the three described eras are summarized in table 1 and expressed both as absolute increases in overall survival due to each treatment and in number of patients needed to treat to save one life compared to no treatment.

**Role of adjuvant chemotherapy: implications and limitations of the metanalytic approach**

Metanalyses of randomized trials, especially those based on individual patient data, provide strong evidence of superiority of a treatment compared to another. However, it must be noted that this approach calculates average treatment-related effects and does not take into account the differential effect that the treatment under consideration has on biologically diverse subsets of tumors. Thus, treatment paradigms based on metanalyses can be the subject of criticism when it comes to their application in the clinical practice.
The latest fully published metanalysis of the EBCGTG suggested that 6 cycles of an anthracycline-based regimen like FAC or FEC (5-fluorouracil, doxorubicin or epirubicin and cyclophosphamide) should be considered the adjuvant chemotherapy treatment of choice in absence of medical contraindications (Early Breast Cancer Trialists' Collaborative Group 2005). Rephrasing this concept, “one regimen (which resulted as the strongest) fits all (patients who are deemed to need adjuvant chemotherapy)”. The alternative CMF-like regimens (cyclophosphamide, methotrexate and 5-fluorouracil), which resulted inferior in terms of efficacy according to the comparisons made in the metanalysis, should be considered suboptimal because lesser efficacy impairs the therapeutic ratio, even in the presence of moderate reduction in the overall toxicities. Furthermore, the same paper consolidated two concepts that had already emerged in previous analyses:

1) The proportional reduction in the risk of relapse and death due to chemotherapy is independent of the biological subset of breast cancer and of the baseline risk of relapse. Its magnitude, however, differs between younger (age <50) and older (age 50-69) women, being much lower in the latter subset (Table 2).

2) In women with hormone-receptor positive breast cancer who are taking also tamoxifen, the benefits of endocrine therapy and chemotherapy are not mutually exclusive and, rather, tend to add each other (Table 2).

The main consequence of these concepts is that all the women with hormone-receptor positive operable breast whose risk of death is beyond a certain threshold can derive some benefit from anthracycline-based adjuvant chemotherapy. The absolute gain in survival varies, however, over a wide range starting from very few percentage points in older women whose baseline risk of death is just beyond that threshold (table 2). This approach, based on average estimates of the effect of chemotherapy, leads inevitably to overtreatment and, consequently, to an increase in the toxic burden of adjuvant therapy. Retrospective analyses of adjuvant clinical trials and new data on tumor biology have
provided grounds to the generation of alternative hypotheses on the efficacy of chemotherapy according to the hormone receptor status of the tumor, which will be addressed in the next chapter.

**Evidence supporting a limited role of adjuvant chemotherapy in hormone-positive breast cancer**

The International Breast Cancer Study Group (IBCSG) trial IX randomized 1715 post-menopausal women with lymphnode negative early breast cancer to tamoxifen for 5 years with or without chemotherapy, which consisted of 3 cycles of “classical CMF” (International Breast Cancer Study Group 2002). Randomization in that study was stratified by ER status, resulting in 23% of patients with ER-negative disease. The overall results of the trial confirmed that 3 courses of CMF improved disease-free survival significantly. However, analyzing the two subsets based on the status of ER (negative vs positive), 3 cycles of CMF added to tamoxifen had a significant impact on both disease-free and overall survival only in ER-negative patients, with virtually no effect in the ER-positive subset (Table 3).

The CALGB conducted, over about two decades, studies aimed at progressively increasing the efficacy of adjuvant chemotherapy by dose and schedule modification and by the introduction of taxanes. Study 8541 showed that both disease-free and overall survival were improved in women receiving a CAF regimen administered at high or moderate dose compared to women receiving a low-dose regimen (Budman et al. 1998). A further step was the addition of four 3-weekly doses of paclitaxel to 4 cycles of AC in the already discussed 9344 study (Henderson et al. 2003). The third step along this incrementalistic path was the CALGB 9741 trial, that compared the same anthracycline and paclitaxel containing regimens administered every 3 or every 2 weeks (Citron et al. 2003). Shortening of the interval between administrations without changing the total dose,
achieved by the use of granulocyte colony stimulating factors, resulted in increased dose-density of chemotherapy. The experimental “dose dense” strategy was associated to increased disease-free and overall survival. Each incrementalistic step pursued in these trials, obtained building on previous experiences, yielded small benefits that added each other into a significant final result. All these studies enrolled patients with both hormone-receptor positive, who received also adjuvant endocrine therapy (mainly tamoxifen), and negative tumors. A recently published retrospective analysis of these studies revealed that only patients with hormone-receptor negative patients achieved significant benefits by increasing the strength of regimens (Table 3) (Berry et al. 2006). For patients with hormone-receptor positive tumors the Kaplan-Meier survival curves comparing lower vs higher strength regimens were superimposable, at least for the initial 4 years after randomization, then started to diverge, resulting in much lower absolute benefits at 5 years compared with women with hormone-receptor negative disease. Although not completely excluding that stronger chemotherapy may be better for patients independently of hormone-receptor status, these results are often cited as a convincing argument against the role of chemotherapy for hormone-positive early breast cancer (Goldhirsch et al. 2005).

Still unpublished, an interesting retrospective analysis of the South Western Oncology Group (SWOG-8814)/Breast Intergroup Trial 0100 trial was presented by Dr. Albain at the 27th San Antonio breast cancer symposium (Albain et al. 2004). This study compared tamoxifen alone with chemotherapy consisting of six cycles of CAF followed by tamoxifen in women older than 65 years, with ER and/or PgR positive tumors and axillary positive lymphnodes. A third arm consisted of chemotherapy and tamoxifen started concomitantly. The overall results of the trial demonstrated that the sequence of CAF and tamoxifen improved 10-year disease-free and overall survival over tamoxifen alone. One analysis focused on patients whose tumors expressed high vs low levels of estrogen receptor
measured by the Allred score (analysis based on 344 patients out of the 1477 enrolled). (Allred et al. 1998) In higher ER-expressors the use of CAF was not associated with a significant improvement in disease-free survival compared with tamoxifen alone. Another analysis focused on HER2 status and number of metastatic axillary lymph-nodes. The authors also found that in patients with HER2-negative disease and with 1-3 involved axillary lymph nodes, disease-free survival was not improved by the use of CAF, compared with tamoxifen alone (analysis based on a total of 385 patients out of the total 1477 enrolled).

That hormone-positive breast cancer is less sensitive chemotherapy is a concept has achieved clear confirmation in neoadjuvant chemotherapy trials, where hormone-receptor status is negatively associated with the likelihood of achieving a pathological complete remission (pCR) (Guarneri et al. 2006). On average, with the last generation of neoadjuvant chemotherapy regimens, pCR rates of 6 to 10% and up to 55% are observed in hormone-receptor positive and negative patients, respectively (Mazouni et al. 2007). Furthermore, recent reports suggest that the higher the percentage of cells expressing hormone-receptors, the lower the likelihood of pCR at the end of neoadjuvant chemotherapy (Colleoni et al. 2008).

**From the 2005 San Gallen Conference onwards: conceptual evolution of adjuvant therapy for hormone-positive breast cancer**

The hypotheses on the marginal role of adjuvant chemotherapy in the treatment of hormone-receptor positive early breast cancer were the foundation of a shift in the paradigm of treatments choices. At the 2005 San Gallen Conference panelists proposed an alternative approach to previously followed one, which called for risk estimation (relapse or death) as the initial step in the decisional process (Goldhirsch et al. 2005).
Conference panelists established that the first step in the algorithm was the assessment of the endocrine responsiveness of the rumor. Through the definitions of “Endocrine responsive”, “Endocrine response uncertain” and “Endocrine unresponsive”, recently renamed “Highly endocrine responsive”, “Incompletely endocrine responsive” and “Endocrine non-responsive”, are categorized patients whose tumors are progressively less likely to benefit from endocrine therapy (Goldhirsch et al. 2007). The definition of these three categories relies mainly, but not exclusively, on the percentage of tumor cells that stain positively for the ER and PgR. Absent staining denotes endocrine unresponsive tumors. High expression of both receptors, together with absence of adverse biological factors like HER2 overexpression/amplification, increased proliferation index or high tumor levels of urokinase-type plasminogen activator/plasminogen activator inhibitor type 1 (uPA/PAI-1) denotes highly endocrine responsive tumors. Incompletely endocrine responsive tumors are characterized by features like either lack of PgR expression and/or hormone-receptor positivity together with adverse biological factors (see above) or extensive axillary lymphnode invasion. Once the target is identified, the San Gallen panelists recommended to evaluate the risk of relapse and to decide about the treatment accordingly. At the latest conference, held in March 2009, panelists considered no longer appropriate risk-categorization to establish separate therapy recommendations (Goldhirsch et al. 2009). The panelists proposed the concept of minimum thresholds to justify a certain therapy. Thus, while any level of hormone receptor expression would justify endocrine therapy, the threshold to add chemotherapy in hormone receptor positive, HER2 negative patients remains more challenging to establish. However, when for one of these patients chemotherapy is perceived to be adequate, the San Gallen panelists were still not able to agree on the “definition of a standard regimen” (Goldhirsch et al. 2009). In our opinion, this uncertainty is coherent with the assumption that strength of the regimen
is not influent in hormone-receptor positive tumors because of their reduced chemosensitivity.

In the following chapters, we will discuss whether this assumption is acceptable in the light of the most recent results of adjuvant chemotherapy studies.

**Introduction of taxanes in the adjuvant treatment of breast cancer: a real step forward?**

One of the most controversial and interesting aspects of the debate around the role of chemotherapy in hormone-receptor positive breast cancer is that they are often defined “less chemosensitive” or “chemorefractory”, but differences in the strength of chemotherapy regimens is rarely accounted for in these evaluations. This view is in part supported by the observations that have been previously summarized, regarding studies with regimens like CMF, anthracycline-based or the CALGB and NSABP data on the studies with paclitaxel added to AC. However, both Peto’s and De Laurentiis’s metanalyses show that there is no difference in the size of benefit of taxanes, expressed as proportional risk reductions, according to age or hormone receptor status. Furthermore, a pooled analysis of the PACS 01 and BCIRG 001 studies revealed that the proportional reduction in the risk of death due to taxanes was almost identical in women with no ER expression and in women whose tumor stained positively in >85% of cancer cells (Andre et al. 2008). These results suggest that the addition of taxanes to anthracyclines seems to overcome of the relative chemorefractoriness of hormone-receptor positive tumors. Thus, according to available data, the taxanes should be considered a step forward in the adjuvant treatment of women with hormone-receptor positive breast cancer, at least in the subsets with positive axillary lymph-nodes. The inclusion of taxanes in the adjuvant treatment is inevitably associated with increased costs and additional treatment related toxicities. With respect to the first issue, the estimated incremental cost-effectiveness ratio
(ICER) of taxane-containing regimens compared to their non-taxane counterparts of equal duration is usually below commonly accepted thresholds (Ward et al. 2007; Younis et al. 2008).

With regard to toxicity, the addition of taxanes may indeed translate into combinations that are more toxic of their non-taxane counterparts. This is certainly true for the TAC regimen, where docetaxel replaced the less toxic 5-fluorouracil, resulting in increased overall toxicity and the need to use of granulocyte colony-stimulating factors as primary prophylaxis of neutropenic fever (Martin et al. 2005; Martin et al. 2006). However, we must point out that this is not the rule for all the taxane-based combinations available for clinical use. For example, the sequential regimen used in the PACS 01 trial was not more toxic than FEC\textsubscript{100}, with a strong suggestion towards less cardiac toxicity due to the lower dose of epirubicin (Roche et al. 2006). Similarly, a sequential regimen of 4 cycles of FEC administered every 3 weeks followed by 8 weekly administrations of paclitaxel resulted slightly less grade 3 and 4 neutropenia, febrile neutropenia, fatigue, nausea, vomiting and stomatitis than 6 cycles of FEC in the GEICAM 9906 study (Martin et al. 2008). Reversible peripheral neuropathy and arthralgia and/or myalgia were observed only in the paclitaxel-containing arm. Results of second-generation clinical trials comparing different schedules of taxanes-based adjuvant chemotherapy are becoming available and will provide additional data to guide the choice of regimens based on efficacy, toxicity and costs (Eierman et al. 2008; Sparano et al. 2008).

In summary, if we accept this reasoning, in a patient with hormone-receptor positive breast cancer who is deemed to be eligible for chemotherapy in addition to endocrine therapy, the reasonable alternative to a taxane-containing regimen should be no-chemotherapy at all. Thus it becomes crucial the accurate identification of those patients for whom chemotherapy offers no benefit and can be avoided.
Treatment tailoring in hormone-positive early breast cancer: a realistic target?

Multigene expression analysis techniques are intensively studied as tools for treatment tailoring in breast cancer as well as in other cancers (Sotiriou & Pusztai 2009). A seminal paper published by Perou et al. showed that breast cancer can be grouped into subgroups defined by distinct gene expression patterns (Luminal A, Luminal B, HER2 and Basal like, named intrinsic subtypes) (Perou et al. 2000). Immunohistochemical profiling reveals that the molecularly defined Luminal A and Luminal B groups include the vast majority of hormone-receptor expressing tumors. Subsequent studies showed that these intrinsic subtypes carry a different prognosis, with luminal A tumors having the best clinical outcome and the basal-like and HER2 subtypes the worst (Sorlie et al. 2001). Concomitantly, prognostic gene signatures were developed in an effort to identify, analyzing the expression of a restricted group of genes, reliable indicators of clinical outcome that could be adopted in the clinical practice. Those that are currently approved for clinical use are grouped in table 4, but several others are currently under investigation (Pusztai 2006). One common aspect of most of these signatures is that they were developed as a pure prognostic tool to distinguish between tumors with extremely good prognosis in the absence of adjuvant treatment or of adjuvant chemotherapy, from those with poor prognosis. Some of these signatures have been shown to outperform clinically based risk-assessment tools on this aspect, leading to a potential reduction of the overtreatment of patients with particularly good prognosis. Furthermore, three of the four commercially available multigene expression analysis tests summarized in table 4 have been specifically developed for patients with hormone-receptor positive disease. Two of these tests can be performed on formalin-fixed, paraffin embedded tumor material and do not require a change in the routine processing of surgical tumor specimens.
One of such tools, the Oncotype DX, merits to be addressed in more details (Paik 2007). This test was developed to answer the following question; “Is it possible to identify a woman with hormone-receptor positive, lymphnode negative breast cancer, for whom it may be necessary something more than just tamoxifen alone?” Among the 16 genes that the Oncotype DX analyzes, some are related to the estrogen receptor (ESR1, PGR, BCL2, SCUBE2), other to cell proliferation (Ki67, Survivin, STK15, CCNB1, MYBL2), and other, like HER2, that are not functionally related. The relative expression of these genes compared to that of 5 reference genes whose expression does not correlate with tumor aggressiveness, is combined by a mathematical formula that results in a continuous score (recurrence score-RS) that is directly proportional to the risk of relapse. The RS has been divided into 3 risk categories by cutoffs that were established studying the clinical outcome of women enrolled in the tamoxifen arm of the NSABP B20 clinical trial (Fisher et al. 1997). The low risk group has been defined by a RS< 18, the intermediate by a RS between 18 and 30 and the high risk by a RS >30.

The prognostic value of the RS was validated in women with hormone receptor positive, lymphnode negative operable breast cancer receiving tamoxifen in the NSABP B 14 trial (Paik et al. 2004). Subsequently, the impact of adding chemotherapy (CMF or MF) to tamoxifen according to RS was studied in patients enrolled in the chemotherapy arm of the NSABP B20 study (Paik et al. 2006), that enrolled women with lymphnode negative, hormone receptor positive breast cancer. The tamoxifen alone arm was used to develop the Oncotype DX. Results of these analyses, which are grouped in table 5, provided evidence for the incorporation of this test in the clinical practice to identify patients at very low risk of developing distant metastases when treated with tamoxifen alone (Harris et al. 2007). The percentage of patients falling into the three risk categories in published studies is summarized in table 6 (Albain et al. 2007; Goldstein et al. 2008; Habel et al. 2006; Paik et al. 2004; Paik et al. 2006). Low-risk patients, account for 40 to 56% of hormone-receptor
positive patients. Aside the clinical implications of these findings, we believe that results with the Oncotype DX demonstrate that the biological diversity of hormone-receptor positive tumors might not be completely resolved by using levels of ER or PgR positivity. On the other hand, metanalyses of gene-signatures reveal that much of the prognostic information that these systems provide relies on the expression of genes related with cell proliferation (Haibe-Kains et al. 2008; Wirapati et al. 2008). Indeed, in patients with hormone-receptor positive HER2-negative disease, high levels of Ki67, a routinely assessed immunohistochemical marker of cell proliferation, confer poor prognosis (Viale et al. 2008) and an advantage when stronger chemotherapy is used (Hugh et al. 2009; Penault-Llorca et al. 2009). These findings revitalize the concept that classical histopathological and immunohistochemical parameters may allow treatment tailoring in a substantial proportion of hormone-receptor positive patients. Validated multigene expression analysis tools like the Oncotype DX or the MammaPrint are useful in uncertain cases, where for example classical parameters are not conclusive (i.e. histopathological grade 2, Ki67 close to the cutoff discriminating low from high proliferation). This view has been recently endorsed by the San Gallen Panelists at the last meeting in 2009 (Goldhirsch et al. 2009).

**Conclusions**

The mainstay of the treatment of hormone-receptor positive breast cancer is endocrine therapy, with diversified options based on patients’ menopausal status. The benefit derived by endocrine therapy is accompanied by an acceptable profile of side effects. Controversy around the use of chemotherapy in hormone-receptor positive is the result of a virtuous effort at sparing toxicities to patients who are unlikely to benefit from chemotherapy. Retrospective analyses of studies conducted in the pre-taxane era and initial experiences with paclitaxel-containing combinations suggested minimal or no benefits at all by adding
chemotherapy to tamoxifen in patients with hormone-receptor positive disease, especially if at low or moderate risk of relapse. At the same time, the concept of endocrine responsiveness has evolved from being simply based on hormone-receptor expression to a more complex reading based on multigene expression analysis studies.

At present time, reliable and accurate evaluation of the classical histopathological and immunohistochemical factors allows the choice of omitting chemotherapy in some patients with low or intermediate risk hormone-receptor positive breast cancer. High expression of both hormone receptors (>50% of the cells), HER2 negativity, G1 histopathological grade and low Ki67 are markers of good prognosis even in the presence of 1 to 3 positive positive axillary lymphnodes. These patients, most of whom carry Luminal A tumors, could be spared chemotherapy because their prognosis is unlikely to be further improved beyond endocrine therapy. However, uncertainty about the benefits of chemotherapy still exists for a substantial proportion of women with hormone receptor positive breast cancer, which causes subjectivity in using pathological findings in decision making. A recent paper showed that at eight National Comprehensive Cancer Network centers, there was a progressive reduction in the use of chemotherapy in patients with hormone-receptor positive disease from 1997 to 2004 (Hassett et al. 2008). This was interpreted as the acceptance of the concept that chemotherapy may be worthless in a proportion of these women. However, a multivariate analysis of factors associated with chemotherapy revealed that, among other independent predictive factors like tumor size, histological grade and lymphnodal status, the institution where the patient was treated was also associated with the likelihood of receiving adjuvant chemotherapy. There was a high variability in chemotherapy use between Institutions, and, in the same Institution, over time. Hopefully, integration of the newer prognostic factors based on multigene expression analysis will help reduce subjectivity in data interpretation and allow physicians a more objective evaluation of the worth of chemotherapy for each single patient.
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Authors contribution

Filippo Montemurro conceived the paper and wrote it.
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Glossary of chemotherapy schedules

AC-Paclitaxel in the NSABP B-28 trial: doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) administered every 3 weeks for 4 cycles, followed by paclitaxel 225 mg/m² administered every 3 weeks for 4 cycles.

AC-Paclitaxel in the CALGB 9344 trial: doxorubicin (60, 75 or 90 mg/m²) and cyclophosphamide (600 mg/m²) administered every 3 weeks for 4 cycles, followed by paclitaxel 175 mg/m² administered every 3 weeks for 4 cycles.

FAC in the BCIRG 001 trial: 5-fluorouracil (500 mg/m²), doxorubicin (50 mg/m²) and cyclophosphamide (500 mg/m²) administered every 3 weeks for 6 cycles

TAC in the BCIRG 001 trial: docetaxel (75 mg/m²), doxorubicin (50 mg/m²) and cyclophosphamide (500 mg/m²) administered every 3 weeks for 6 cycles with antibiotic prophylaxis.

FEC_{100} in the PACS 01 trial: 5-fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (500 mg/m²), all given intravenously every 3 weeks for 6 cycles.

FEC_{100}-Docetaxel in the PACS 01 trial: 3 cycles of FEC (same as above) followed by docetaxel (100 mg/m²) every 3 weeks for 3 cycles

FEC-Docetaxel in the UK TACT trial: 5-fluorouracil (600 mg/m²), epirubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every 3 weeks for four cycles followed by docetaxel (100 mg/m²) every 3 weeks for four cycles.

FEC in the TACT trial: same as above for 8 cycles

Epirubicin and CMF in the TACT trial: epirubicin (100 mg/m²) every 3 weeks for 4 cycles and cyclophosphamide (600 mg/m²), methotrexate (40 mg/m²) and 5-fluorouracil (600 mg/m²) on days 1 and 8 every 4 weeks for 4 cycles.
**Classical CMF:** cyclophosphamide (100 mg per square meter given orally every day for 14 days) methotrexate (40 mg per square meter) and fluorouracil (600 mg per square meter) given intravenously on days 1 and 8 of the cycle.

**CAF-high dose in the CALGB 8541 trial:** Cyclophosphamide (600 mg per square meter), doxorubicin (60 mg per square meter) and fluorouracil (500 mg per square meter), both given intravenously on days 1 every 4 weeks for 4 cycles. The same dose of 5-fluorouracil was repeated on day 8 of each cycle regardless of hematologic values.

**CAF-moderate dose in the CALGB 8541 trial:** Cyclophosphamide (400 mg per square meter), doxorubicin (40 mg per square meter) and fluorouracil (400 mg per square meter), both given intravenously on days 1 every 4 weeks for 6 cycles. 5-fluorouracil was repeated on day 8 of each cycle.

**CAF-low dose in the CALGB 8541 trial:** Cyclophosphamide (300 mg per square meter), doxorubicin (30 mg per square meter) and fluorouracil (300 mg per square meter), both given intravenously on days 1 every 4 weeks for 4 cycles. 5-fluorouracil was repeated on day 8 of each cycle.

**CAF in the Breast Intergroup Trial 001:** Cyclophosphamide (100 mg per square meter), given orally every day for 14 days; epirubicin (60 mg per square meter) and fluorouracil (500 mg per square meter), both given intravenously on days 1 and 8 every 4 weeks for six cycles (with routine antibiotic prophylaxis).

**FEC in the GEICAM 9906 trial:** fluorouracil (600 mg per square meter), epirubicin (90 mg per square meter), and cyclophosphamide (600 mg per square meter), all given intravenously every 3 weeks for 6 cycles.

**FEC-Paclitaxel in the GEICAM 9906 trial:** 4 cycles of FEC (same as above) followed by paclitaxel 100 mg/m² every week for 8 weeks.
Table 1. Progress in adjuvant chemotherapy from CMF to Taxane and Anthracycline based regimens

<table>
<thead>
<tr>
<th>Comparison</th>
<th>10-year probability of death(^1)</th>
<th>Absolute improvement in 5-year survival(^1)</th>
<th>Theoretical NNT to save one life</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF vs No adjuvant chemotherapy</td>
<td>32.2% vs 36.4%</td>
<td>4.2%</td>
<td>24</td>
</tr>
<tr>
<td>Anthracycline based-regimens vs CMF-like regimens</td>
<td>27.0% vs 31.3%</td>
<td>4.3%</td>
<td>11*</td>
</tr>
<tr>
<td>Taxane vs Anthracycline-no taxane</td>
<td>25.9% vs 31.0%</td>
<td>5.1%</td>
<td>9*</td>
</tr>
</tbody>
</table>

\(^1\)Data presented by Richard Peto at the 30\(^{th}\) San Antonio Breast Cancer Symposium in 2007 (Peto 2007).

NNT, number needed to treat.

*NNT to save one life has been calculated using the 10-year probability of death of patients not receiving chemotherapy (36.4%) as reference. For example, the NNT of Anthracycline-based therapy compared to no chemotherapy has been calculated as follows: 1/(0.364-0.27)=11. A lower NNT indicates higher clinical impact because less patients receive the treatment without deriving a survival benefit from it. These figures need to be taken with caution because they do not derive from a direct comparison between treatment (anthracycline-based and taxane-based regimens) and no treatment.
Table 2. Estimated effects of 6 months of anthracycline-based chemotherapy, 5 years of tamoxifen, or both on 15-year breast cancer mortality (%), in the absence of other causes of death

<table>
<thead>
<tr>
<th>Proportional reduction of the risk of death</th>
<th>Absolute increase in 15-year survival as a function of the baseline risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td><strong>Chemotherapy alone (ER+ and -)</strong></td>
<td></td>
</tr>
<tr>
<td>Anthracycline (age &lt; 50)</td>
<td>38%</td>
</tr>
<tr>
<td>Anthracycline (age 50-69)</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Endocrine therapy (ER+)</strong></td>
<td></td>
</tr>
<tr>
<td>TAM (any age)</td>
<td>31%</td>
</tr>
<tr>
<td>Anthracycline + TAM (age &lt; 50)</td>
<td>57%</td>
</tr>
<tr>
<td>Anthracycline + TAM (age 50-69)</td>
<td>45%</td>
</tr>
</tbody>
</table>

HR, hazard ratio; ER, estrogen receptor; TAM, tamoxifen; M, 15-year breast cancer death risk.

This table summarizes the estimated effects of chemotherapy, endocrine therapy or both according to age. Absolute 15-year increases in breast cancer survival are calculated based on the proportional reduction in the risk of death for each category of age and treatment considering two hypothetical situations of 15-year mortality risk in the absence of adjuvant therapy: 12.5% (M=12.5), which is the estimated mortality of a low-risk breast cancer patient (i.e. lymphnode negative, no adverse biological factors) and 50% (M=50), which is the estimated mortality of a high-risk patient (i.e. lymphnode positive).

Modified from Early Breast Cancer Trialists Collaborative Group 2005
Table 3. Summary of influential subset analyses addressing the role of adjuvant chemotherapy according to hormone receptor status

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Comparison</th>
<th>Absolute gain in 5-y DFS in the whole population</th>
<th>Absolute gain in 5-y DFS in HR-patients*</th>
<th>Absolute gain in 5-y DFS in HR+ patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBCSG IX</td>
<td>Post-menopausal, node-negative (N 1669)</td>
<td>Classical CMF X 3→T vs T alone</td>
<td>4% for CMF→T vs T</td>
<td>15% for CMF→T vs T**</td>
<td>1% for T vs CMF→T**</td>
</tr>
<tr>
<td>CALGB 8541</td>
<td>N-positive patients (N 1477)</td>
<td>CAF-HD vs CAF-MD vs CAF-LD</td>
<td>10% and 5% for CAF-HD and ID vs CAF-LD</td>
<td>13.9% for CAF-HD vs CAF-LD</td>
<td>6.6% for CAF-HD vs CAF-LD</td>
</tr>
<tr>
<td>CALGB 9344</td>
<td>N-positive patients (N 3121)</td>
<td>AC→P vs AC</td>
<td>5% for AC→P vs AC</td>
<td>8.2% for AC→P vs AC</td>
<td>2.1% for AC→P vs AC</td>
</tr>
<tr>
<td>CALGB 9741</td>
<td>N-positive patients (N 2005)</td>
<td>q3wks vs q2 wks doxorubicin, cyclophosphamide and paclitaxel</td>
<td>7% for q2wks vs q3wks</td>
<td>22.8% for q2wks vs q3wks**</td>
<td>7% for q2wks vs q3wks**</td>
</tr>
</tbody>
</table>

HR, hormone receptor; DFS, disease-free survival; HD, high dose; ID, intermediate dose; LD, low dose
*High expression according to the Allred score
**Test of interaction of HR status and efficacy of the experimental regimen was statistically significant
<table>
<thead>
<tr>
<th>Name</th>
<th>Oncotype DX</th>
<th>MapQuant Dx</th>
<th>Theros</th>
<th>MammaPrint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Assay</td>
<td>21-gene recurrence score</td>
<td>Genomic Grade</td>
<td>2-gene ratio of HOXB13 to IL17R (H/I) and molecular-grade index</td>
<td>70-gene assay</td>
</tr>
<tr>
<td>Technique</td>
<td>Quantitative RT-PCR</td>
<td>DNA microarrays</td>
<td>Quantitative RT-PCR</td>
<td>DNA microarrays</td>
</tr>
<tr>
<td>Type of tumor material required</td>
<td>Formalin-fixed, paraffine-embedded</td>
<td>Fresh or frozen</td>
<td>Formalin-fixed, paraffine-embedded</td>
<td>Fresh or frozen</td>
</tr>
<tr>
<td>Indication</td>
<td>To predict the risk of recurrence in patients with ER-positive, node-negative disease treated with tamoxifen; to identify patients with a low risk of recurrence who may not need adjuvant chemotherapy</td>
<td>To restratify grade 2 tumors into low-risk grade 1 or high-risk grade 3 tumors, specifically for invasive, primary, ER-positive grade 2 tumors</td>
<td>To stratify ER-positive patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy</td>
<td>To aid in prognostic prediction in patients &lt;61 yr of age with stage I or II, node-negative disease with a tumor size of 5 cm</td>
</tr>
<tr>
<td>Provider</td>
<td>Genomic Health</td>
<td>Ipsogen</td>
<td>Biotheranostics</td>
<td>Agenda</td>
</tr>
</tbody>
</table>

RT-PCR, reverse-transcriptase-polymerase chain reaction. Modified from Sotiriou 2009
Table 5. Validation of the OncotypeDX in patients with hormone-receptor positive, lymphnode negative breast cancer.

<table>
<thead>
<tr>
<th>Aim of the study</th>
<th>Study population</th>
<th>Treatment (N of patients)</th>
<th>10-year rates of distant metastases according to Recurrence score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation of the prognostic value</td>
<td>NSABP B 14</td>
<td>Tamoxifen (668)</td>
<td>6.8% 14.3% 30.5%</td>
</tr>
<tr>
<td>Study of chemotherapy related benefit</td>
<td>NSABP B 20</td>
<td>Tamoxifen (227)</td>
<td>3.2% 9.1% 39.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tamoxifen + CMF or MF</td>
<td>4.4% 10.9% 11.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(424)</td>
<td></td>
</tr>
</tbody>
</table>

CMF: cyclophosphamide, methotrexate and 5-fluorouracil. MF: methotrexate and 5-fluorouracil
**Table 6. Proportion of patients according to each recurrence score group in published series**

<table>
<thead>
<tr>
<th>Study</th>
<th>Low (RS&lt;18)</th>
<th>Intermediate (RS 18-30)</th>
<th>High (RS &gt;30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-14 (Paik <em>et al.</em> 2004)</td>
<td>51%</td>
<td>22%</td>
<td>27%</td>
</tr>
<tr>
<td>NSABP B-20 (Paik <em>et al.</em> 2006)</td>
<td>54%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Kaiser Permanente (Habel <em>et al.</em> 2006)</td>
<td>56%</td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td>ECOG 2197 (Goldstein <em>et al.</em> 2008)</td>
<td>46%</td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>SWOG 8814/INT0100 (Albain <em>et al.</em> 2007)</td>
<td>40%</td>
<td>28%</td>
<td>32%</td>
</tr>
</tbody>
</table>

RS, recurrence score; NSABP, national surgical adjuvant breast and bowel project; ECOG, eastern cooperative oncology group; SWOG, south western oncology group.