Recent advances in adjuvant systemic therapy for early-stage breast cancer

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Introduction

More than 429 000 European women are diagnosed with breast cancer annually [1]. The vast majority of women present with early-stage disease and receive adjuvant systemic therapy following surgical resection. Although rates of breast cancer-related mortality have continued to decline in Europe since the early 1990s, many women diagnosed with early-stage breast cancer will die due to disease recurrence in spite of adjuvant systemic therapy [2]. In addition, many women experience long-term side-effects from adjuvant breast cancer therapy. The fundamental imperative of early breast cancer management is to optimize adjuvant systemic therapy, in order to improve long-term survival and minimize toxicity. In this manuscript we review recently presented data concerning some important open questions in adjuvant systemic therapy for early-stage breast cancer.

Adjuvant chemotherapy

What is the role of taxanes?

Taxanes are amongst the most active chemotherapeutic agents used to treat metastatic breast cancer. Their activity in metastatic disease, novel mechanism of action and non-cross resistance with anthracyclines provide a sound rationale for testing their activity in the adjuvant setting. Results are now available from 16 randomized trials comprising >30 000 women with early-stage breast cancer in which taxane- and non-taxane-containing regimens have been compared. Based on these trials three meta-analyses have been conducted. The addition of taxanes appears to improve disease-free and overall survival (OS) in women with early-stage breast cancer, irrespective of age, menopausal status, hormonal receptor expression and lymph node involvement [3–5]. Preliminary results from the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview using individual patient-based data from trials which randomized >20 000 women to taxane- versus non-taxane-containing regimens also indicate that the inclusion of taxanes in adjuvant therapy improves recurrence-free survival [hazard rate (HR) = 0.83, 2P < 0.00001] [6]. However, the recent presentation of the results from two large well-conducted clinical trials has once again challenged the role of taxanes in the adjuvant setting.

The National Cancer Institute of Canada (NCIC) MA.21 trial randomized 2014 women with lymph node-positive disease aged <60 to six cycles of cyclophosphamide–epirubicin–5-fluorouracil (CEF), four cycles of doxorubicin–cyclophosphamide followed by four cycles of paclitaxel every 3 weeks (AC→T) or four cycles of dose-dense epirubicin–cyclophosphamide followed by paclitaxel every 3 weeks for four cycles (ddEC→T) [7, 8]. At a median follow-up of 30 months, the taxane-containing AC→T regimen was inferior to the standard anthracycline arm for disease-free survival (DFS) (3-year DFS 85% versus 89%, HR = 1.49, P = 0.0005). There was no difference in DFS between the ddEC→T and CEF arms (3-year DFS 90% versus 89%, HR = 0.86, P = 0.46). At the initial interim analysis, OS data were too immature for reporting.

More recently, the United Kingdom Taxotere as Adjuvant Therapy (TACT) trial was presented at the 2007 San Antonio Breast Cancer Symposium. Between February 2001 and July 2003, 4162 women in the UK were randomized to a standard regimen of eight cycles of 5-FU–epirubicin–cyclophosphamide (FEC) or four cycles of epirubicin followed by four cycles of cyclophosphamide–methotrexate–5FU (E→CMF) at the discretion of the participating center versus the experimental regimen of four cycles of FEC followed by four cycles of docetaxel (FEC→D) [9]. In contrast to the MA.21 trial, ~20% of the patients enrolled in the TACT had high-risk lymph node-negative disease. After a median follow-up of 52 months, 92% of the anticipated DFS events had occurred. There was no difference between the taxane and non-taxane arms with regard to DFS (5-year DFS 74.7% FEC→D versus 73.9% control, HR = 0.97, P = 0.62) or OS (5-year OS 82.0% FEC→D versus 81.8% control, HR = 0.98, P = 0.76). The taxane arm exhibited greater toxicity, in the form of febrile neutropenia, lethargy, neuropathy and musculoskeletal complaints. Retrospective subgroup analysis did not identify markers that were predictive of a benefit from the taxane-containing regimen, such as lymph node status, hormonal receptor status, histological grade or age. Similar to the retrospective analysis of three successive Cancer and Leukemia Group B (CALGB) trials [10], there was a suggestion in the TACT trial that patients with HER-2 overexpression and absent oestrogen receptor (ER) expression may benefit from the inclusion of a taxane [DFS HR = 0.70, 95% confidence interval (CI) 0.49–1.01]. However, this was not a predefined hypothesis in the TACT trial and there was only a suggestion of benefit for taxane inclusion in the...
node-positive patients with ER-negative, HER-2-positive disease. Furthermore, these findings are in opposition to retrospective subgroup analyses from the PACS 01 and GEICAM 9906 trials, which did not find that HER positivity was a predictive marker of benefit from taxane-based therapy [11, 12].

When the results of the MA.21 and TACT study are considered, it is difficult to make definitive conclusions regarding the optimal role of taxanes in adjuvant therapy for early-stage breast cancer. Unfortunately, all of the first-generation taxane trials were performed in an era where entry criteria for adjuvant trials was based upon anatomical definitions of relapse risk, such as lymph node involvement, rather than an understanding of the fundamental molecular heterogeneity of breast cancer [13, 14].

The 2000 EBCTCG overview analysis demonstrated that nodal status and tumor size do not correlate with the relative benefit from adjuvant chemotherapy are less pronounced, the 2000 overview suggested that the chemotherapy was more effective in women with ER-negative rather than ER-positive disease [15]. To date, there do not appear to be any predictive markers that clearly define subgroups of patients likely to benefit from the inclusion of a taxane, despite several years of efforts in translational research studies. HER-2 overexpression/amplification, p53 status and microtubule-associated parameters all have a potential role but so far reach only level 3 or 4 evidence.

The preliminary presentation of the 2005 EBCTCG overview at the 2007 San Antonio Breast Cancer Symposium (SABCS) subdivided the first-generation taxane trials on the basis of the ‘strength’ of the anthracycline-containing arm [6]. Using this classification, it did not appear that there was any clear difference between the trials that compared taxanes with ‘standard’ or ‘low-strength’ regimens (HRs = 0.86 and 0.82, respectively). However, the trials with ‘standard’ strength anthracycline comparators involved only 6000 of the >20 000 women included in the overview. Additionally, so far the EBCTCG overview includes only ~20 000 of the >50 000 women who entered adjuvant taxane trials. Hence, the results of the next overview cycle, hopefully including all patients entered in taxane adjuvant trials, are eagerly awaited. It will be interesting to see whether a difference based upon the strength of the anthracycline comparator arm emerges with the eventual inclusion of the >4000 patients enrolled in the TACT trial. The E→CMF regimen used as the standard comparator in the TACT trial is one of the few regimens that has been demonstrated to be directly superior to classical oral CMF [16].

Based upon the existing evidence, it is reasonable to consider the inclusion of a taxane in women with a high risk of relapse with incomplete or absent endocrine sensitivity. Furthermore, in HER-2-positive breast cancer the use of taxanes is strongly recommended, not only based on the available data suggesting a potential increased efficacy but mainly to decrease the risk of cardiotoxicity since these patients are candidates for adjuvant trastuzumab.

how should taxanes be administered?
Although the precise role of adjuvant taxane therapy remains controversial, much has recently been learned about the optimal type and schedule of taxane administration. The ECOG 1199 randomized 4950 women with lymph node-positive or high-risk lymph node-negative early-stage breast cancer to four cycles of AC followed by four different strategies of taxane administration: 3-weekly paclitaxel at 175 mg/m², weekly paclitaxel at 80 mg/m², 3-weekly docetaxel at 100 mg/m² and weekly docetaxel at 35 mg/m² [17]. After a median follow-up of 64 months, weekly paclitaxel at 80 mg/m² and 3-weekly docetaxel at 100 mg/m² were superior to 3-weekly paclitaxel at 175 mg/m² in terms of DFS [17]. These findings echo results from earlier studies in the metastatic setting: both CALGB 9840 and the Anglo-Celtic Trial IV demonstrated that the weekly paclitaxel was superior to 3-weekly paclitaxel for response rate and time to progression (TTP) [18, 19]. Similarly, the TAX 311 trial performed by the US Oncology group showed that the 3-weekly docetaxel at 100 mg/m² improved TTP and OS when compared with 3-weekly paclitaxel at 175 mg/m² [20].

can we safely avoid anthracyclines?
In the most recent update of the EBCTCG overview, anthracyclines provide a 4.6% absolute decrease in 10-year breast cancer-related mortality when compared with CMF-based regimens of similar duration [6]. The experience from clinical trials suggests that the excess risk of cardiac morbidity associated with anthracycline administration in early breast cancer is minimal [15]. In the 2000 EBCTCG overview, anthracycline-based regimens were associated with an annual risk of cardiac mortality of 0.08%/year as compared with 0.06%/year in patients treated with non-anthracycline-based regimens [15]. However, the recent evaluation of population-based registries has questioned the long-term cardiac safety of anthracyclines, particularly for older women with early-stage breast cancer [21, 22]. Recently, the US Oncology 9735 trial, which randomized women to four cycles of the non-anthracycline-containing docetaxel cyclophosphamide (TC) regimen or four cycles of AC, was updated at the 2007 SABCS [23]. The initial publication of the trial after a median follow-up of 5.5 years demonstrated an improvement in 5-year DFS for TC over AC [24]. There was a suggestion of a benefit in OS; however, this did not reach statistical significance. With further follow-up to 7 years, TC is now associated with a statistically significant improvement in OS (6-year OS 88% versus 84%, HR = 0.73, P = 0.045). This trial establishes the TC regimen as a viable option for women with low-to-intermediate risk disease, particularly for women at risk of developing anthracycline-induced cardiomyopathy, although its role in the management of high-risk endocrine non-responsive disease is still a matter of debate.

A recent meta-analysis of eight trials randomizing 6564 women with early-stage breast cancer to anthracycline versus non-anthracycline-based regimens suggests that the benefit of anthracycline administration is limited to the subpopulation of women with HER-2-positive disease [25]. Biologically, anthracyclines are known to inhibit topoisomerase IIα, whose gene (TOP2A) lies adjacent to the HER-2 amplicon on chromosome 17 and is co-amplified in ~35% of HER-2-positive breast cancer. Subgroup analysis of the BCIG 006 trial, which randomized women with HER-2-positive disease to...
doxorubicin–cyclophosphamide followed by docetaxel (AC→T), or AC→T with concurrent trastuzumab, or the non-anthracycline-containing docetaxel–carboplatin–trastuzumab (TCH) regimen, demonstrated that women with TOP2A and HER-2 co-amplification had similar outcomes when treated with either AC→T, AC→TH or TCH [26, 27]. As a result, some have questioned the role of adjuvant anthracyclines in the management of early-stage breast cancer [28]. They argue that women with TOP2A and HER-2 co-amplification, which comprise ~8% of the total breast cancer population, are the only subgroup that appears to benefit from anthracycline administration. Moreover, the BCIRG 006 trial shows that anthracyclines can be avoided even in this small subgroup by using the non-anthracycline trastuzumab-containing TCH regimen. However, it should be kept in mind that the results of the BCIRG 006 trial are immature, as only 462 DFS events had occurred at the time of the second interim analysis in 2006 [26]. Furthermore, the original trials which demonstrated the superiority of anthracycline-based regimens over CMF did not prospectively mandate HER-2 or TOP2A testing and all subgroup analyses on the basis HER-2 and/or TOP2A expression were retrospective and exploratory in nature. The role of TOP2A as a predictive marker of response to anthracyclines has for the moment level 3 to 2 evidence and needs to be further validated before it can be used in clinical practice. Until then, patients should not be deprived of anthracycline-based adjuvant therapy, which has proven efficacy, if their risk assessment so determines.

**adjuvant trastuzumab**

is there a chink in trastuzumab’s armour?
The advent of trastuzumab therapy in the adjuvant management of HER-2-positive breast cancer is widely regarded as a major breakthrough [29]. To date, results are available from five studies which have randomized 11 650 women with early-stage HER-2-positive breast cancer to trastuzumab versus non-trastuzumab-based adjuvant chemotherapy. All five of these trials have demonstrated remarkably similar findings, namely, that the inclusion of trastuzumab approximately produces a 50% improvement in DFS and a 33% improvement in OS, regardless of type of chemotherapy administration or the sequence of trastuzumab delivery [30–33]. Recently, the results of the NCCTG 9831/NSABP B31 joint analysis and the HERA trial were updated with a median follow-up of 2.9 years and 2 years, respectively [34, 35]. With further follow-up, the benefit of trastuzumab is maintained. At the 2007 SABCS, however, the first trial which did not demonstrate a benefit for adjuvant trastuzumab therapy in HER-2-positive disease was presented. The PACS 04 study randomized 3010 women with node-positive disease to either six cycles of epirubicin and docetaxel (ED) or six cycles of 5-FU–epirubicin–cyclophosphamide (FEC-100). The 526 included women with HER-2-positive disease underwent a second randomization to either 1 year of adjuvant trastuzumab or no adjuvant trastuzumab after the completion of their primary cytotoxic chemotherapy [36]. After a median follow-up of 40 months, there was no difference in either DFS or OS for the trastuzumab- versus the non-trastuzumab-containing arms (HR for DFS 0.86, P = 0.41). Of note, 10% of women randomized to the trastuzumab arm were never treated with adjuvant trastuzumab therapy. Although it is not entirely clear why the PACS 04 trial did not demonstrate a degree of benefit similar to those seen in the other adjuvant trastuzumab trials, clinicians must consider the results of this 526-patient trial within the context of the results observed from the 11 650 women included in previously reported adjuvant trastuzumab studies. Further updates of the five other adjuvant trials with longer follow-up, and the HERO results on 1 versus 2 years of adjuvant trastuzumab are eagerly awaited.

**adjuvant hormonal therapy**

should tamoxifen be continued beyond 5 years?
Women with ER-positive breast cancer have a long-term ongoing risk of recurrence following surgery for their primary breast cancer which surpasses the risk of recurrence of ER-negative breast cancer at 15 years follow-up. Long-term follow-up from successive ECOG trials and the EBCTCG overview demonstrates that there are as many recurrences in years 6–15 after surgery as in years 1–5 [15, 37, 38]. The MA.17 trial showed that switching to the aromatase inhibitor (AI) letrozole after 5 years of adjuvant tamoxifen resulted in a 43% reduction in the risk of recurrence after a median follow-up of 2.4 years for post-menopausal women [39]. This trial provides proof of the principle that women with ER-positive breast cancer remain sensitive to anti-hormonal strategies beyond 5 years of adjuvant tamoxifen. The issue of whether there might be a benefit to continuing tamoxifen beyond 5 years has been debated for a number of years. The NSABP B-14 trial randomized 1172 women with node-negative disease to either continued tamoxifen for an additional 5 years or no further therapy after 5 years of adjuvant tamoxifen therapy suggested that there was no additional benefit to continued tamoxifen [40]. In contrast, subgroup analysis of smaller ECOG studies suggested that 10 years of tamoxifen might be beneficial in women with ER-positive, node-positive disease [40]. The results from the Adjuvant Tamoxifen, Longer Against Shorter (ATLAS) trial were presented for the first time at the 2007 SABCS. In this trial involving 11 500 women, 10 years of adjuvant tamoxifen was associated with a statistically significant 11% decrease in the risk of recurrence [41]. Neither OS data nor toxicity were reported at the symposium. Although most clinicians will likely continue a switch to an AI after 5 years of tamoxifen in post-menopausal women based on the MA.17 results, the data from ATLAS suggest that there may be a role for continued tamoxifen in young women who remain premenopausal after 5 years of tamoxifen or in post-menopausal women who are unable to tolerate an AI.

is the strategy of using an upfront AI durable and safe?
Long-term results from the ATAC trial after a median follow-up of 100 months are now available [42]. As with the comparison of tamoxifen with no hormonal therapy from the
EBCTCG overview [6], the absolute benefit of anastrozole over tamoxifen in preventing DFS events in post-menopausal women increased over time. At 5 years, 16.4% of patients in the tamoxifen arm had experienced DFS events as compared with 13.9% in the anastrozole arm; in comparison, there were 29.9% women in the tamoxifen arm who had experienced DFS events versus 25.8% in the anastrozole arm at the 9-year mark. Even with prolonged follow-up, no improvement in OS was yet observed in favor of anastrozole therapy (HR = 0.97, P = 0.7). Interestingly, the excess fracture risk in the anastrozole arm observed during active therapy (annual fracture rate of 2.93%/year in anastrozole arm versus 1.90%/year in the tamoxifen arm) disappeared after the completion of 5 years of therapy (1.56%/year versus 1.51%/year, P = 0.97). Although AI-induced bone loss remains an important concern in selecting appropriate hormonal therapy for individual patients, this observation demonstrates that there is no carryover effect for anastrozole-induced fragility fracture. Likewise, with extended follow-up there remained no significant difference in cardiovascular mortality or morbidity between the anastrozole and tamoxifen groups.

Patients prescribed AIs frequently develop arthralgias as a limiting toxicity. The ATAC experience with anastrozole-induced arthralgias was updated at the 2007 SABCS [43]. Joint symptoms were more commonly observed with anastrozole than tamoxifen (36.5% versus 30.9%, P < 0.001). Upon retrospective review, anastrozole therapy, previous hormone therapy, chemotherapy, North America or United Kingdom as country of origin, body mass index (BMI) ≥ 30 were significantly associated with joint symptoms. The clinical importance of AI-related arthralgia has been extensively reported this last year, both inside and particularly outside clinical trials. In the latter situation it seems to affect about one-third of patients and is an important cause of non-compliance. Patient education before starting on an AI therapy is crucial, as is the understanding that tamoxifen is an excellent option in case of intolerance. Another interesting study presented at SABCS suggested that women who develop joint symptoms on a non-steroidal AI, such as anastrozole or letrozole, may not experience similar joint symptoms after switching to an alternative non-steroidal AI [44].

**who benefits from an upfront AI?**

In addition to concerns regarding joint symptoms and accelerated bone loss, upfront AI therapy is significantly more expensive than adjuvant tamoxifen. There is significant uncertainty regarding which post-menopausal patients benefit from upfront therapy with an AI versus a switch to an AI following an initial period of tamoxifen therapy. The most recent St Gallen Consensus also acknowledges that there may still be a role for 5 years of upfront tamoxifen followed by extended adjuvant therapy with an AI in particular subgroups of women with early-stage breast cancer [45]. Thus, determining which patients will benefit from a strategy of using an AI upfront remains a challenge. An initial exploratory retrospective subgroup analysis of the ATAC trial suggested that the differential benefit of anastrozole over tamoxifen treatment was greater in women with ER-positive and progesterone receptor (PR)-negative tumors than for ER-positive and PR-positive tumors [46]. This theory that PR negativity could be used as a predictive marker to select patients who might benefit from AI therapy was supported by preclinical observations that lack of PR expression was associated with a dysfunctional ER signaling pathway [47]. More recently, after central pathological review of tumor specimens, ER-positive and PR-negative status was no longer associated with a differential benefit from anastrozole therapy in the ATAC trial [48]. This observation is consistent with the findings from other large adjuvant AI studies, such as the BIG 1-98 [49] and ABCSG 8/ARNO 95 [50] trials. More recent data suggest that markers of increased cellular proliferation, such as Ki-67, may identify women likely to benefit from an upfront AI strategy. At the 2007 SABCS, Viale et al. [51] centrally analyzed tumor specimens from a subset of women enrolled in the BIG 1-98 trial. In their analysis, women with high Ki-67 expression, defined as an immunohistochemical labeling index of >11%, benefited more from adjuvant letrozole over tamoxifen monotherapy (4-year DFS 90% versus 82%) than women with low Ki-67 expression (93% versus 91%, interaction P-value = 0.09). Although compelling, this finding requires further validation in an independent data set before proliferation can be used to identify women who should be treated with adjuvant AI therapy. Furthermore, gene expression profiling studies have consistently shown that high proliferation identifies tumors likely to respond to adjuvant chemotherapy. The best way to integrate all these findings to guide decision-making is still under investigation.

Beyond pharmacodynamic considerations, there is growing evidence that pharmacogenomics may identify women unlikely to benefit from adjuvant tamoxifen monotherapy. Tamoxifen is metabolized to its active metabolite endoxifen through the cytochrome P450 2D6 (CYP2D6) enzyme. There are genotypic variants of CYP2D6 which produce different serum levels of endoxifen. Retrospective studies have shown that low-tamoxifen metabolizing CYP2D6 activity is associated with an increased risk of relapse with adjuvant tamoxifen therapy [52, 53] and a decreased response rate in the metastatic setting [54]. Paradoxically, high-tamoxifen metabolizers, the subgroup of women most likely to benefit from tamoxifen, experience more hot flashes [52] and are more likely to discontinue tamoxifen therapy because of toxicity [55]. There is also evidence that CYP2D6 genotype is associated with the efficacy of tamoxifen chemoprevention in women at high risk of developing breast cancer [56] and co-administration of CYP2D6 inhibitors, such as the antidepressant paroxetine, is associated with reduced serum endoxifen levels [57]. Although there is no prospective evidence to support tailoring hormonal therapy on the basis of tamoxifen metabolism, it seems reasonable to consider AI therapy in post-menopausal women with an increased risk of relapse where CYP2D6 testing is available.

**conclusions**

Today, there are more therapeutic choices available for early-stage breast cancer than for any other tumor type. Despite a broad armamentarium of therapy, there remains considerable
uncertainty regarding the optimal therapeutic strategy for individual patients. Although the precise role of taxanes is somewhat uncertain, based upon the data from first-generation taxane trials it is reasonable to consider taxane therapy in women with an elevated risk of relapse where endocrine sensitivity is absent or incomplete. In the future, it may be possible to limit anthracyclines to particular subgroups of patients with specific molecular alterations, such as co-amplification of HER-2 and TOP2A. However, further prospective data are required before anthracyclines can be routinely omitted in patients who do not harbor such biomarkers.

For patients with HER-2-positive disease, adjuvant trastuzumab therapy has a clearly established benefit, in spite of the recent negative findings from the PACS 04 trial. The updated results from the ATAC study with a median follow-up of 100 months demonstrate that upfront AI therapy produces a small, but statistically significant, benefit in terms of DFS over tamoxifen monotherapy in post-menopausal women. PR negativity is not a reliable predictive biomarker. In the future, elevated proliferation indices and pharmacogenomic profiling may guide decisions regarding optimal strategy for hormonal therapy in post-menopausal women.

For premenopausal women and those post-menopausal who do not tolerate an AI, prolonged use of tamoxifen beyond 5 years is an acceptable option, provided that women continue to be monitored for development of endometrial cancer.

disclosures

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references

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