Annals of Oncology 26: 1533–1546, 2015
doi:10.1093/annonc/mdv221
Published online 4 May 2015

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

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Received 27 April 2015; accepted 28 April 2015

The 14th St Gallen International Breast Cancer Conference (2015) reviewed substantial new evidence on locoregional and systemic therapies for early breast cancer. Further experience has supported the adequacy of tumor margins defined as 'no ink on invasive tumor or DCIS' and the safety of omitting axillary dissection in specific cohorts. Radiotherapy trials support irradiation of regional nodes in node-positive disease. Considering subdivisions within luminal disease, the Panel was more concerned with indications for the use of specific therapies, rather than surrogate identification of intrinsic subtypes as measured by multiparameter molecular tests. For the treatment of HER2-positive disease in patients with node-negative cancers up to 1 cm, the Panel endorsed a simplified regimen comprising paclitaxel and trastuzumab without anthracycline as adjuvant therapy. For premenopausal patients with endocrine responsive disease, the Panel endorsed the role of ovarian function suppression with either tamoxifen or exemestane for patients at higher risk. The Panel noted the value of an LHRH agonist given during chemotherapy for premenopausal women with ER-negative disease in protecting against premature ovarian failure and preserving fertility. The Panel noted increasing evidence for the prognostic value of commonly used multiparameter molecular markers, some of which also carried prognostic information for late relapse. The Panel noted that the results of such tests, where available, were frequently used to assist decisions about the inclusion of cytotoxic chemotherapy in the treatment of patients with luminal disease, but noted that threshold values had not been established for this purpose for any of these tests. Multiparameter molecular assays are expensive and therefore unavailable in much of the world. The majority of new breast cancer cases and breast cancer deaths now occur in less developed regions of the world. In these areas, less expensive pathology tests may provide valuable information. The Panel recommendations on treatment are not intended to apply to all patients, but rather to establish norms appropriate for the majority. Again, economic considerations may require that less expensive and only marginally less effective therapies may be necessary in less resourced areas. Panel recommendations do not imply unanimous agreement among Panel members. Indeed, very few of the 200 questions received 100% agreement from the Panel. In the text below, wording is intended to convey the strength of Panel support for each recommendation, while details of Panel voting on each question are available in supplementary Appendix S2, available at *Annals of Oncology* online.

Key words: surgery, radiation therapy, systemic adjuvant therapies, early breast cancer, St Gallen Consensus

introduction

The fourteenth St Gallen International Breast Cancer Conference, held for the first time in neighboring Vienna, Austria, confirmed, and extended the recommendations of earlier reports.

This report is focused on providing a practical approach to the allocation of available therapies to individual patients in the

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light of the most recent and reliable information from clinical trials, laboratory insights and the expert opinions of a large international faculty. To this end, attention is given to tumor factors and the condition of the host. Tumor factors are primarily the presence or absence of targetable features such as hormone receptors and HER2, and the metastatic potential, as reflected in measures of proliferation and anatomic extent of disease. Patient factors include menopausal status, age, comorbidity, and patient preference.

St Gallen 2015: news and progress

A large part of the world has an increasing incidence of breast cancer, but limited resources to treat it. The majority of new cases and the majority of breast cancer deaths now occur in less developed regions of the world [1]. Many of the countries in the less developed regions have low health expenditure per capita, which renders the use of expensive laboratory tests and treatments inaccessible to the majority of patients worldwide (http://data.worldbank.org/indicator/SH.XPD.PCAP?display=map accessed 29.12.2014). The development of effective treatments which are less expensive is thus a priority [2].

The Panel welcomed a number of recent clinical trial results, especially the SOFT and TEXT trials clarifying the role of ovarian function suppression with tamoxifen or exemestane in the endocrine treatment of premenopausal patients, and the POEMS trial confirming the protective value of an LHRH agonist for ovarian function [3–5]. A curious paradox emerged in the evidence for local therapies. Surgical management continued its trend to less extensive surgery without compromise of the outcome [6, 7], but recent radiotherapy trials in node-positive disease found superior disease control with extended radiation fields which included regional lymph node areas [8, 9]. No such benefit was seen in a population-based study [10]. Hypofractionated shorter course radiotherapy has become accepted as a standard option [11, 12] offering increased patient convenience and reduced resource usage.

A recent update of the overview of adjuvant aromatase inhibitors (AIs) (Dowsett M, personal communication) in postmenopausal patients found that, on average, patients have fewer recurrences while assigned AI than while assigned tamoxifen during those periods when the treatments differed, although there was no significant difference in breast cancer mortality in trials comparing 5 years of an AI to the sequence of tamoxifen followed by an AI.

breast cancer subtypes

Extensive genomic analysis of breast cancers discloses four coherent groups [13], similar to the intrinsic subtypes defined by gene expression profiling [14]. Subtypes can be defined by multiparameter molecular tests such as the PAM-50 [15] or MammaPrint/BluePrint [16]. However, in clinical practice, the key question is not the separation of the molecularly defined intrinsic subtypes, but the discrimination between patients who will or will not benefit from particular therapies. Several of the multiparameter molecular markers have been used for this purpose [17, 18]. Because in much of the world, such tests may not be available for logistic or financial reasons, surrogate approaches have been developed using more widely available immunohistochemical (IHC) tests for estrogen receptor, progesterone receptor together with IHC or *in situ* hybridization tests for HER2 overexpression or amplification. Ki-67 is used as an alternative marker of proliferation albeit with lesser analytical validity than molecular testing [19, 20].

Standard pathological features seem adequate to define clinically useful groups such as triple-negative, hormone receptor-negative and HER2-positive and hormone receptor-positive\and HER2-positive tumors for which treatment recommendations are seldom controversial. It is among the patients with 'luminal' disease, defined by the presence of ER and/or PgR and negative HER2, that uncertainty about optimal treatment most commonly arises, as clinicians seek to avoid overtreatment and undertreatment. A survey of patterns of the use of chemotherapy in such patients [21, 22] showed that there was a substantially different use of chemotherapy in different geographical areas.

The various multiparameter molecular marker assays all include genes reflecting proliferative activity: indeed, it has been suggested that the majority of the prognostic information in these tests comes from the proliferative genes included [23]. IHC measurement of proliferative activity using the Ki-67 assay has proved controversial. There can be little doubt that Ki-67 scores carry robust prognostic information [24], and that high values predict the benefit of addition of cytotoxic chemotherapy [25], but definition of a single useful cut point has proved elusive both because Ki-67 displays a continuous distribution [26], and as a result of analytic and preanalytic barriers to standardized assessment [27]. Other news presented at the meeting is summarized in Table 1.

panel deliberations

On the Saturday morning, the Panel reviewed a series of some 200 questions developed by iterative consultation over the months preceding the conference. Voting on most questions was in the format yes, no, or abstain, with some presented as multiple mutually exclusive alternatives. Abstaining was recommended if a Panel member had a conflict of interest, felt that there was insufficient evidence to support an opinion or that he or she lacked the relevant expertise. Detailed voting records for each of the questions put to the Panel are provided in the supplementary Appendix S2, available at *Annals of Oncology* online.

surgery of the primary

The Panel strongly endorsed recent findings that the minimal acceptable surgical margin was 'no ink on invasive tumor or DCIS'.

This conclusion applies regardless of tumor characteristics such as lobular histology, extensive intraductal component, young age, multifocality or multicentricity, and unfavorable biological subtype [7].

A clear majority of the Panel agreed that multifocal and multicentric tumors could be treated with breast conservation, provided the above margin clearance was obtained and whole-breast radiotherapy was planned.

Following neoadjuvant chemotherapy, the Panel did not consider it necessary to resect the entire area of the original primary if downstaging had occurred.

Table 1. Recent research findings presented at the 14th International Conference on Primary Therapy of Early Breast Cancer and their implications for patient care

Field or treatment	Status of research/implications for patient care
Surgical management	Local regional recurrence is becoming less frequent over recent decades [28]. Meta-analysis of surgical series showed no further benefit from margins beyond 'no ink on invasive tumor or DCIS' [29]. This conclusion applies regardless of tumor characteristics such as lobular histology, extensive intraductal component, young age, and unfavorable biological subtype [7]. Avoiding axillary dissection for patients with one or two macrometastatic lymph nodes [30, 31] proved safe in a large institutional series, confirming the applicability of randomized trial approaches (ACOSOG Z011, AMAROS) for the majority of women with T1 and T2 clinically node-negative breast cancer [6].
Extent of locoregional radiotherapy	Two recent radiotherapy trials in node-positive disease found superior disease control with extended radiation fields which included regional lymph node areas [8, 9].
Prognostic value of multiparameter molecular markers	Oncotype DX® was predictive of late distant recurrence in NSABP B-14 [32]. However, it was not predictive of late distant recurrence after endocrine therapy in the ATAC study, while PAM-50 ROR score® [17, 33] and the immunohistochemically based IHC4® each remained prognostically significant beyond 5 years of endocrine treatment [34, 35]. Likewise, EndoPredict® was prognostically significant beyond 5 years in ABCSG trials 6 and 8, particularly when combined with clinical factors [36]. Breast Cancer Index® was prognostic for early and late distant recurrence in two series [37].
Reducing the risk of chemotherapy-induced premature ovarian failure	In the recently reported POEMS study [5], OFS with LHRH analogue during chemotherapy for patients with receptor-negative breast cancer reduced the incidence of premature ovarian failure, confirming the report of Del Mastro et al. [38], but contrary to the findings of the ZORO study of the German Breast Group [39]. In the POEMS study, such treatment also increased the rate of subsequent successful pregnancies and did not compromise disease outcomes [5].
Observational registry data	Because only a small fraction of patients are entered on randomized clinical trials, evolving standardized registry datasets offer information which may be more typical of the entire patient population. Although biases can never be entirely removed from such datasets, useful information has been described in many clinical settings including oncology [40].
Cancer genomics	Multiple recent studies have described the landscape of the expanding list of mutations and other genetic abnormalities in patients with recurrent breast cancer. Apart from a small number of frequently mutated genes, there is a long 'tail' of genetic abnormalities, which are infrequent but may cluster in particular pathways such as the JUN kinase pathway [41].
Genomic tools for marker assessment	Genomic tests added little to IHC for the assessment of ER and only slightly more for PgR, while there was more substantial disagreement between conventional and genomic testing for HER2 [42, 43].
Intrinsic subtypes	Attempts to reproduce the intrinsic subtype distinction between 'luminal A-like' and 'luminal B-like' using conventional pathology have proved impractical. While it is possible to refine definitions to more closely approximate intrinsic subtypes [19, 44, 45], this may not provide the clinically useful threshold to guide treatment choice. Intrinsic subtypes within HER2-positive disease are heterogeneous and, in one study, this was reflected in potential differences in predicting degree of response to trastuzumab [46]. The difference between the hormone receptor-negative and positive cohorts within HER2-positive disease is illustrated by the consistently higher clinical response (pCR) to neoadjuvant therapies for the hormone receptor-negative cohort [47, 48]. Although a majority of triple-negative breast cancers show the basal-like subtype [49], the distinction between these and other types of triple-negative breast cancer is important for choice of chemotherapy in that carboplatin is as effective as docetaxel in basal-like but less so in other intrinsic subtypes in the metastatic setting [50]. Further dissection of subtypes within triple-negative breast cancer reveals seven distinct groupings, which differ markedly in their clinical response to neoadjuvant chemotherapy [51]. Preclinical studies also show heterogeneity of response to other agents in cell lines of the different triple-negative subtypes [52], though this subclassification is not yet ready for clinical application.
Tumour-infiltrating lymphocytes (TILs)	TILs are most often found in triple-negative (TN), HER2-positive, and other highly proliferative breast cancers, and have been associated with increased pCR, longer disease-free survival (DFS), and improved overall survival (OS), independent of other prognostic factors [53, 54] in some studies, though not among patients treated with trastuzumab in the N9831 trial [55].

Continued

Table 1. *Continued*

Field or treatment	Status of research/implications for patient care
Immune-related pathways	Preclinical studies underline the importance of inflammation and the immune landscape in the stroma, and point to the additional benefit of combining treatments aimed at the immune system (such as anti-IL6) with small molecules such as gefitinib, which inhibit the EGF receptor otherwise enhanced [56]. Immune-targeted drugs may be useful, with recent data available on PD-1 inhibition [57–59].
Targeting CDK 4/6	Palbociclib, a CDK 4/6 inhibitor, given with letrozole showed superior clinical efficacy when compared with letrozole alone as first-line treatment in the PALOMA-1/TRIO-18 randomized phase II trial in metastatic breast cancer [60].
Targeting DNA repair pathways	Patients with deficient DNA repair based on BRCA 1 or BRCA 2 mutation showed high pCR rates to platinum salts [61, 62], and carboplatin is significantly more active than doctaxel in patients with BRCA mutations treated in the metastatic setting [63].
Targeting the PI3K pathway	The combination of the PIK3CA-alpha-specific inhibitor BYL719 and fulvestrant appears synergistic in preclinical models [64].
Targeting the FGFR pathway	Preliminary studies with the FGFR inhibitors dovitinib [65] and lucitanib [66] show promising response rates but substantial toxicity.
Germline genetics	In a small observational study, tamoxifen was associated with a reduced risk of contralateral breast cancer in patients with BRCA 1 and BRCA 2 mutations where the index cancer was ER-positive or ER-negative [67].
Primary prevention	Recent data have emphasized the role of previous benign pathology with atypia and (although to a lesser extent) even without atypia as a risk factor for breast cancer incidence [68].
ER and PgR testing	A large single-institution experience suggests that equivocal ER staining between 1% and 9%, more commonly seen among young patients, those with higher grade or HER2-positive or PgR-negative tumors, tracks prognostically more closely with ER absent disease in terms of recurrence-free survival [69]. Since these patients did not receive endocrine therapy, information is not available on the predictive value of these equivocal ER levels.
Overcoming endocrine therapy resistance	Combining endocrine agents and blockers of growth factors might be a useful strategy to reverse estrogen receptor-targeted therapy resistance [70].
Ki-67 determination	Extensive studies support the prognostic value of Ki-67, but clinical validation has proved difficult. While high and low values are reproducible and clinically useful, there appears to be no optimal cut point, at least to predict pCR along the continuum of Ki-67 levels [71, 72]. International collaboration has led to improvements in concordance of the Ki-67 scoring [27, 73]. Image analysis may help to reduce variability [74].
Neoadjuvant systemic therapies	An improved pCR rate was observed with carboplatin for patients with triple-negative disease [75, 76]. Such improvement was not observed for HER2-positive disease [50, 76]. An improved pCR rate was also observed in triple-negative breast cancer using nab-paclitaxel instead of solvent-based paclitaxel [50]. pCR rates were higher in patients with lymphocyte predominant breast cancer, either triple-negative or HER2-positive, who were treated with carboplatin [77]. PIK3CA mutation was associated with inferior pCR rates to anti-HER2 therapies in several neoadjuvant studies [78–80]. Neoadjuvant endocrine therapies usually take longer to achieve tumor response and pCR rates are generally low. Treatment may continue until maximal response [81]. However, failure to lower Ki-67 offers early identification of a group of patients who should be considered for switch to alternative therapies [82, 83]. Although the neoadjuvant neo-ALTTO trial was clearly positive and supported dual HER2 blockade [84], the adjuvant ALTTO study (using a variety of different chemotherapy regimens) [85] is widely regarded as negative. These apparently conflicting results may not be as divergent as commonly perceived [86]. The hazard ratio in ALTTO of 0.84 comparing dual-blockade with trastuzumab alone [85] was much as expected [86] and the *P* value of 0.048 is interpreted as nonsignificant because the statistical analysis plan divided alpha between the dual-inhibition comparison and that involving the sequential administration of trastuzumab and lapatinib.

Continued

Table 1. *Continued*

Field or treatment	Status of research/implications for patient care
Surgery	A large US population-based study of more than 200 000 women noted that 7% underwent contralateral prophylactic mastectomy (CPM). Although a small survival benefit was observed [87], information was not available on BRCA status, which is known to be both a motivation for CPM and a marker for increased benefit from such surgery. Thus, selection bias could not be adequately addressed in this registry study [88]. There has been a substantial increase in the use of CPM over the past two decades in the United States, particularly in women <40 [89]. In Europe, the trend is less marked [90, 91]. Sentinel node biopsy is feasible and accurate after neoadjuvant chemotherapy and allows precise assessment of pCR [92–95]. In patients with nodal involvement at presentation, the false-negative rate of sentinel node biopsy is highly correlated with the number of sentinel nodes retrieved. Breast conservation after neoadjuvant chemotherapy is feasible even when the disease is multifocal or multicentric, provided that the margins are free of disease [96].
Radiation therapy	Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens [11, 12]. Hypofractioned regimens involving 15 or 16 fractions are now widely accepted as standard of care [97, 98]. Observational data from a population-based registry suggest that radiotherapy to the internal mammary nodes may be associated with a survival benefit in node-positive breast cancer [99].
Adjuvant systemic endocrine therapies in premenopausal patients	For premenopausal women with endocrine responsive disease, results from the SOFT and TEXT trials indicate that the combination of OFS (mainly using triptorelin) and tamoxifen or OFS and AI should be considered for women at higher risk of recurrence such as those remaining premenopausal after chemotherapy; those with multiple positive nodes; and those aged under 35 with appropriate disease-associated risks [3, 4]. Given the potential long-term toxicity of OFS and the lack of a demonstrated survival advantage for this strategy to date and indeed an adverse overall survival finding in ABCSG 12 using anastrozole [100], patient preference and treatment tolerance should be strongly considered in initial and subsequent decisions regarding OFS. Patient-reported outcomes in three endocrine therapy studies [101–103] showed distinct and substantial impact on vasomotor, menopausal, and sexual symptoms. There was no difference seen in overall measures of quality of life between the various therapies. A composite risk score was developed for premenopausal patients in the SOFT and TEXT trials and demonstrated that more intensive therapies such as OFS and exemestane were particularly beneficial for patients at higher risk [104].
Adjuvant systemic endocrine therapies in postmenopausal patients	In BIG 1–98, the original composite risk score which predicted 5-year DFS [105] was also prognostic for disease outcomes beyond 5 years. Late recurrences did not vary according to treatment allocation during the first 5 years [104].
Lifestyle and obesity	Obesity has been associated with poor breast cancer outcomes. The use of anastrozole (but not letrozole) in the adjuvant or extended adjuvant setting may be associated with less benefit in obese women [106].
Adjuvant systemic cytotoxic chemotherapy	A study in patients not selected on the basis of hormone receptor, HER2 or menopausal status with 0–3 lymph nodes involved, showed no advantage for six cycles compared with four of the same regimen [107]. A study of bone marrow neoplasms following systemic breast cancer therapy showed a slightly higher incidence (0.4%–0.5% at 10 years) than had previously been appreciated [108]. Neurotoxicity was present at the completion of taxane-based chemotherapy in one-quarter of patients, and one-third of these had persistent symptoms 1–3 years later [109]. The incidence of cardiac toxicity following chemotherapy and anti-HER2 treatment with trastuzumab did not increase with extended follow-up in the HERA trial [110].
Adjuvant anti-HER2 therapy	A phase II study of adjuvant paclitaxel and trastuzumab, without anthracycline, showed excellent outcome in node-negative, HER2-positive, pT1b and pT1c tumors. Despite the absence of a control group in this study, the regimen is now widely accepted as a standard of care for patients with small, node-negative, HER2-positive tumors [111].
Young women	Age was neither prognostic nor predictive for the impact of trastuzumab in the HERA trial [91]. LHRH agonist therapy during chemotherapy proved effective to protect against premature ovarian failure and preserve fertility in young women with ER-negative breast cancer undergoing chemotherapy [5, 112]. A global observational trial to assess the safety of interrupting endocrine therapy to allow attempted pregnancy is in progress [112].

surgery of the axilla

In the light of recent trial results, the Panel considered the situation of patients with macrometastases in one or two sentinel nodes. The Panel was unanimous that following mastectomy such patients required axillary dissection if no radiotherapy were planned, but was almost exactly equally divided if mastectomy were to be followed by radiotherapy. A clear majority of the Panel would accept the omission of axillary dissection following conservative resection with standard tangent radiotherapy planned, and virtually all would do so if the radiotherapy were planned to use high tangents including the lower axilla.

In a patient clinically node positive at presentation who downstages after neoadjuvant chemotherapy, the Panel considered that sentinel node biopsy was appropriate, but that, in this situation, axillary lymph node dissection was required if even one sentinel node were positive. False-negative rates, however, remain high unless three or more sentinel nodes are examined.

radiation therapy

Radiotherapy courses involving hypofractionation were considered appropriate irrespective of age for patients without prior chemotherapy or clinical lymph node involvement. A bare majority of the Panel would accept hypofractionated radiotherapy for patients with axillary lymph node involvement or prior chemotherapy.

Following breast-conserving surgery, the Panel considered that radiation should be limited to breast only if the nodes were negative. The Panel was in favor of at least some regional nodal radiotherapy if the axillary nodes were positive, and a substantial minority would extend this to include the internal mammary nodes [99]. In post-meeting discussions, several Panel members suggested that adverse pathology should identify patients with lower nodal burden requiring radiotherapy.

Following mastectomy, the Panel considered that radiotherapy should be standard for patients with tumor size 5 cm or greater, those with a positive macrometastatic sentinel node biopsy but no axillary dissection, and for patients with one to three involved nodes and adverse pathology. In the absence of adverse pathology, patients with one to three involved nodes could be treated without post mastectomy radiotherapy, though a slim majority would include such treatment of patients aged <40 years. The Panel considered that the same indications for radiotherapy as described above applied after axillary dissection without prior sentinel node biopsy even if less than eight nodes were examined.

If given, the Panel felt that post mastectomy radiotherapy should include the chest wall and regional nodes with most of those voting prepared to omit the internal mammary nodes. After immediate breast reconstruction, the Panel felt that radiotherapy should include the lymph nodes and the reconstructed breast in most cases.

Interestingly, although the Panel did not consider that surgical resection of the original area of tumor was necessary after downstaging with neoadjuvant systemic therapy, they did consider that radiotherapy following neoadjuvant chemotherapy should in general be directed to the extent of disease before such therapy.

pathology

As in previous St Gallen meetings, the Panel was of the strong opinion that the distinction between strongly endocrine responsive, low proliferation, good prognosis 'luminal A-like' and less endocrine responsive, higher proliferation, poorer prognosis 'luminal B-like' (HER2-negative) tumors could be derived from IHC tests for ER, PgR and Ki-67, though the use of Ki-67 required knowledge of local laboratory values. (The Panel used these terms as a shorthand in classifying hormone receptor-positive disease into luminal A-like and luminal B-like subsets, though it recognized that IHC tests do not accurately measure true intrinsic subtypes.) The corollary was that a clear majority of the Panel did not believe that multiparameter molecular markers were required for this distinction. A majority of the Panel was prepared to accept a threshold value of Ki-67 within the range of 20%–29% to distinguish 'luminal B-like' disease, though about one-fifth of the Panel felt that Ki-67 should not be used at all for this distinction. Only a quarter of the Panel believed that subtype determination could be replaced by risk scores derived from multiparameter molecular markers.

A clear majority of the Panel did not accept the presence of tumor-infiltrating lymphocytes (TILs) as either a prognostic or predictive marker.

The Panel considered the role of multiparameter molecular marker assays for prognosis separately in years 1–5 and beyond 5 years, and their value in selecting patients who require chemotherapy. Oncotype DX®, MammaPrint®, PAM-50 ROR® score, EndoPredict®, and the Breast Cancer Index® were all considered usefully prognostic for years 1–5. Beyond 5 years, the Panel was divided almost equally on the prognostic value of Oncotype DX (despite the available data from NSABP Trial B-14 [32]); EndoPredict® (despite the report of Dubsky et al. [36]); and Breast Cancer Index (despite the report of Zhang et al. [37]). (All these reports show the respective tests to be prognostic beyond 5 years.) PAM50 ROR® score was agreed to be clearly prognostic beyond 5 years, and a clear majority rejected the prognostic value of MammaPrint® in this time period. Only Oncotype DX® commanded a majority in favor of its value in predicting the usefulness of chemotherapy. Clinically, tests which are prognostic, but not specifically predictive of the efficacy of cytotoxic therapy, are commonly used to make decisions about such therapy. This is done on the grounds that they may define a group of patients with a prognosis so good that even if chemotherapy were similarly proportionately effective as in higher risk patients the absolute benefit may be thought insufficient to justify such treatment. Similarly, a test result indicating a worse prognosis may be used to justify the use of effective but more toxic endocrine therapy such as OFS plus AI or more intensive or prolonged chemotherapy.

adjuvant endocrine therapy of premenopausal patients

In the light of recently published results from the SOFT and TEXT trials, the Panel considered treatment recommendations for two clinical scenarios. The first involved a 42-year-old patient with node-negative, grade 2, T1, ER-positive tumor not receiving chemotherapy. A large majority of the Panel would treat such a patient with tamoxifen alone. The second scenario

involved a 34-year-old patient with lymph node-positive, grade 3, T1, ER-positive disease who remained premenopausal after adjuvant chemotherapy. An overwhelming majority of the Panel would advise OFS for this patient, and a large majority would use this with exemestane rather than tamoxifen.

More generally, the Panel considered that factors arguing for inclusion of OFS were age 35 or less; persisting premenopausal estrogen level after adjuvant chemotherapy; or the involvement of four or more axillary nodes. A lesser majority would add grade 3 disease or an adverse result from a multiparameter molecular marker test as indications for OFS.

Factors arguing for the use of an AI plus OFS rather than tamoxifen plus OFS were (overwhelmingly) the involvement of four or more nodes, with lesser majorities accepting age 35 or less; grade 3; or the adverse result of a multiparameter molecular marker test as supporting such treatment. The Panel was almost evenly divided as to whether a persisting premenopausal estrogen level after adjuvant chemotherapy should favor an AI rather than tamoxifen. As a supplementary question, the Panel was asked, 'if you decide to give OFS are you more likely to recommend tamoxifen or an AI?' with a majority favoring AI.

The Panel considered that if OFS were included the optimal duration of such therapy should be 5 years, and that extended endocrine therapy for a total of 10 years should be considered for premenopausal patients initially node-positive or with other adverse pathology.

adjuvant endocrine therapy of postmenopausal patients

The Panel was almost unanimous that some postmenopausal patients can be treated with tamoxifen alone. However, virtually all Panel members regarded the involvement of four or more nodes; grade 3 pathology; or high Ki-67 as arguing for the inclusion of an AI at some point. A lesser majority also felt that HER2 positivity argued in favor of inclusion of an AI, but the Panel did not consider that age <60 should indicate AI therapy. If an AI is used, the Panel was virtually unanimous that it should start up front in patients at higher risk, while the Panel was evenly divided on whether it should be used up front in all patients. The Panel was comfortable to contemplate switching from an AI to tamoxifen after 2 years if necessary.

The Panel was virtually unanimous that following 5 years of adjuvant tamoxifen, patients with initially node-positive disease should continue endocrine therapy to 10 years regardless of menopausal status, but did not consider such extension indicated for initially node-negative disease. A clear majority favored extension to 10 years for patients with grade 3 tumors; high Ki-67; and for patients premenopausal at baseline who became postmenopausal during 5 years of tamoxifen.

The Panel then considered the more complex situation of patients whose initial 5 years of adjuvant therapy had involved a switch from tamoxifen to an AI. A clear majority was in favor of continuing AI therapy to a total cumulative AI duration of 5 years.

Following initial therapy consisting of 5 years of a straight AI, the Panel was evenly divided between recommendations for 3–5 years of tamoxifen; 3–5 more years of an AI; or no further endocrine treatment.

adjuvant cytotoxic chemotherapy

Pending the results of ongoing randomized trials, and notwithstanding the Oxford Overview results [113], the Panel was strongly of the opinion that relative indications for inclusion of adjuvant cytotoxic chemotherapy for patients with 'luminal' disease types were grade 3 histology; 4 or more positive nodes; low hormone receptor staining; high Ki-67; and extensive lymphovascular invasion, but the majority did not believe that one to three positive nodes or age <35 were indications for such treatment.

A clear majority of the Panel believed that 'luminal A-like' phenotype was less responsive to chemotherapy. They would not add such treatment based on T size; lymphovascular invasion; or the involvement of one to three lymph nodes in such patients. However, the Panel almost unanimously recommended chemotherapy when four or more nodes are involved, presumably since the risk of undertreatment is deemed greater in such patients.

The Panel did not believe that chemotherapy should be recommended in all patients with 'luminal B-like' disease. Specifically, it could be omitted in cases with low scores on Oncotype DX®; MammaPrint®; PAM-50 ROR® score; or EndoPredict®. The Panel was evenly divided about whether intermediate Oncotype DX® score should be regarded as an indication for chemotherapy.

When cytotoxic chemotherapy is indicated for luminal disease, the specific choice of regimen depends on the position within the spectrum of degree of endocrine responsiveness and risk of relapse. On average, for 'luminal B-like' tumors, the Oxford overview supports the inclusion of both an anthracycline and a taxane [113], while in 'luminal A-like' tumors, there is little evidence of an advantage compared with older regimens such as AC and CMF [114]. If given, chemotherapy for 'luminal B-like' disease should not extend beyond four courses of the same treatment, especially, for patients with a lower burden of disease. The addition of taxanes should be considered for patients with more extensive disease burden. A slim majority considered that there was a high-risk group for which dose-dense therapy with G-CSF support should be preferred.

In triple-negative disease, the Panel considered that the chemotherapy should include an anthracycline and a taxane. Despite the lack of randomized trial evidence, the Panel would consider a platinum-based regimen in the presence of BRCA mutation, but a large majority felt that standard anthracycline and taxane-based therapy was appropriate for such patients. Platinum-based therapy should not be routinely used in patients without BRCA mutation. The Panel was divided about the value of dose-dense therapy with growth factor support.

In patients with HER2-positive, stage 2 disease, the Panel was almost unanimous that chemotherapy was required and should in general contain an anthracycline and a taxane, with the anti-HER2 therapy starting concurrent with the taxane.

The Panel next considered patients with stage 1, HER2-positive disease. A clear majority felt that anti-HER2 therapy was not required in patients with T1a disease, while a large majority would include such treatment of T1b, and all Panel members would treat patients with T1c disease. A clear majority of the Panel was willing to accept the combination of paclitaxel and trastuzumab without anthracycline as a reasonable option for stage 1 patients and a maximum tumor diameter of 1 cm thought to require therapy. The Panel was divided about

whether such treatment was appropriate for stage 1 patients with a tumor >1 cm, with a slim majority favoring anthracycline/taxane-based therapy for such patients.

adjuvant anti-HER2 therapies

Pending results from the ongoing APHINITY trial, the Panel did not support dual HER2 blockade by the addition of either pertuzumab or lapatinib to trastuzumab for postoperative adjuvant therapy.

neoadjuvant cytotoxic chemotherapy for luminal disease

The Panel did not generally support neoadjuvant cytotoxic therapy for patients with 'luminal A-like' tumors, but would contemplate it if conservative surgery would not otherwise be feasible. In patients with 'luminal B-like' (HER2-negative) tumors, the Panel was more closely divided, but only a minority would recommend such treatment for the majority of cases.

neoadjuvant systemic therapy for stage 2 HER2-positive disease

The majority of the Panel supported dual anti-HER2 therapy with taxane, trastuzumab, and pertuzumab as 'an acceptable regimen' for such patients.

neoadjuvant systemic therapy for patients with triple-negative tumours

The clear majority of the Panel favored anthracycline and taxane-based treatment of such patients, and would not support the use of high-dose alkylating agents or platinums. (The Panel was not asked specifically about neoadjuvant platinum-based therapy in the presence of known BRCA mutation, but later agreed that such therapy should not be routinely used for patients without BRCA mutation.)

neoadjuvant endocrine therapies

The Panel was strongly of the opinion that neoadjuvant endocrine therapy without cytotoxics was a reasonable option for postmenopausal patients with endocrine responsive disease. Indeed, the Panel considered that the preferred treatment of postmenopausal women with 'luminal A-like' breast cancer not suitable for breast-conserving surgery at diagnosis was endocrine rather than cytotoxic neoadjuvant therapy. The Panel considered that such treatment should continue for either 4–8 months or until maximal response.

bisphosphonates

The Panel was divided about the use of bisphosphonates such as zoledronic acid or clodronate to improve disease-free survival. In postmenopausal patients, a slim majority would support such treatment. Only a minority would support such treatment in premenopausal patients receiving LHRH and tamoxifen. The Panel was virtually unanimous in rejecting such treatment of premenopausal patients not receiving LHRH and would not support the use of denosumab as a substitute for bisphosphonates.

elderly patients

The Panel considered that there was no absolute age limit for the use of standard chemotherapy regimens. Rather, the use of such treatments should depend on disease characteristics, comorbidity, life expectancy, and patient preference.

Similarly, the Panel considered that there was no age at which radiation therapy otherwise indicated should be omitted.

young patients

The Panel considered that testing for BRCA 1 and BRCA 2 mutations is indicated in patients aged <40 years and those with a strong family history, but was divided about whether this should be extended to testing for high-risk mutations in other genes. The Panel would extend testing to patients up to the age of 50 with triple-negative disease even in the absence of a family history.

The Panel considered that fertility preservation by ovarian tissue or oocyte conservation should be offered upon request for patients aged <40.

The Panel strongly supported the use of OFS during chemotherapy for receptor-negative disease to preserve ovarian function and fertility.

high-risk mutations

The presence of a BRCA 1 or BRCA 2 mutation was thought to influence locoregional and neoadjuvant treatment, but not adjuvant therapy.

breast cancer diagnosed during pregnancy

For patients whose breast cancer was diagnosed during pregnancy premature delivery should be avoided if possible, and standard chemotherapy regimens should be offered during the third or second trimester, but not anti-HER-2 or endocrine therapies. The Panel considered that breast conservation was a suitable option; that sentinel node biopsy using radioisotope was safe; and that immediate post mastectomy reconstruction could be considered.

attempting pregnancy after breast cancer

The Panel acknowledged the possibility of interrupting endocrine therapy after 18–30 months to allow attempted pregnancy, but only in the absence of high-risk features.

male breast cancer

Recognizing that the current adjuvant treatment of males with breast cancer is tamoxifen, the Panel did not support the use of AIs, either with or without LHRH agonists.

lifestyle factors to reduce the risk of recurrence

The Panel supported the use of an exercise regimen and weight loss (or at least avoidance of weight gain). They did not recommend any specific dietary advice to improve prognosis, but a majority would support vitamin D supplementation for those shown to be vitamin D deficient.

summary of treatment recommendations

surgery

Meta-analysis of surgical series showed no further benefit from margins beyond 'no ink on invasive tumor or DCIS', including patients with lobular histology, extensive intraductal component, young age, or unfavorable biological subtype.

Axillary dissection can be avoided for patients with one or two macrometastatic lymph nodes.

radiotherapy

Disease control and survival are improved when radiation fields were extended to include regional lymph node areas in patients with node-positive disease.

neoadjuvant systemic therapies

While acknowledging that neoadjuvant therapy has not been shown to produce survival outcomes superior to those of postoperative adjuvant therapy alone, there is increasing support for neoadjuvant cytotoxic therapy in Stage II triple-negative disease and for combined chemotherapy and anti-HER2 therapy in patients with HER2-positive disease and large tumors. In patients with luminal disease, there is less indication for neoadjuvant cytotoxic chemotherapy unless it is given to enable breast conservation, but the option of neoadjuvant endocrine therapy also exists for many of these patients.

postoperative systemic adjuvant therapies

As summarized in Tables 2 and 3, most patients with triple-negative disease should receive cytotoxic chemotherapy containing an anthracycline and a taxane, though a slim majority of the Panel felt that platinum-based therapy might be considered for a patient with known BRCA mutation.

In patients with HER2-positive, node-negative disease and T-size <2 cm, a nonanthracycline regimen comprising paclitaxel and 1 year of trastuzumab is appropriate, while for more extensive disease treatment should commence with anthracycline and be followed by concurrent taxane and trastuzumab, with the trastuzumab continued for a total of 1 year.

Patients with hormone receptor-positive and HER2-positive disease will require endocrine therapy appropriate to their menopausal status in addition to cytotoxics and anti-HER2 therapy.

For patients with hormone receptor-positive and HER2-negative disease, a spectrum exists in degree of risk and of responsiveness to cytotoxic chemotherapy. Those at lower risk with strongly positive receptors can be adequately treated with endocrine therapy alone. Consideration of the relative level of hormone receptor expression and proliferation are important to determine prognosis and the need for adjuvant chemotherapy. The multiparameter assays, either immunohistochemically based 'IHC4' as carried out by Cuzick and Dowsett or one of several multiparameter molecular marker assays, such as OncotypeDx®, MammaPrint®, Endopredict®, PAM50 ROR®, and BCI®, each appears to identify a group of patients for whom prognosis is so favorable that even if chemotherapy is effective, the benefits of treatment are so small that they do not outweigh the risks. For patients with worse anatomical prognostic features, such as the presence of a T4 lesion, high Ki-67, low hormone receptor staining or four or more positive axillary lymph nodes, even those with favorable multiparameter molecular assay results may have a sufficiently high risk of recurrence to justify adjuvant chemotherapy.

Endocrine therapy for premenopausal patients at low risk should comprise tamoxifen for 5 years, while those at higher risk should be considered for OFS and the substitution of exemestane for tamoxifen. In patients who have completed 5 years of adjuvant tamoxifen therapy and are regarded as being at higher risk, it is appropriate to consider continuing endocrine

Table 2. Treatment-oriented classification of subgroups of breast cancer

Clinical grouping	Notes
Triple-negative	Negative ER, PgR, and HER2
Hormone receptor-negative and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-negative luminal disease as a spectrum:	ER and/or PgR positive ≥1%[a]
High receptor, low proliferation, low tumor burden (luminal A-like)	Multiparameter molecular marker 'favorable prognosis' if available. High ER/PgR and clearly low Ki-67[b]. Low or absent nodal involvement (N 0–3), smaller T size (T1 T2).
Intermediate	Multiparameter molecular marker 'intermediate' if available[c]. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
Low receptor, high proliferation, high tumor burden (luminal B-like)	Multiparameter molecular marker 'unfavorable prognosis' if available. Lower ER/PgR with clearly high Ki-67[b]. More extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3).

[a]ER values between 1% and 9% were considered equivocal. Thus, endocrine therapy alone cannot be relied upon for patients with these values.
[b]Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.
[c]Not all multiparameter molecular marker tests report an intermediate score.

Table 3. Postoperative adjuvant systemic treatment recommendations

Clinical grouping	Type of therapy	Notes on therapy
Triple-negative	Cytotoxic chemotherapy including anthracycline and taxane	Platinum-based chemotherapy may be considered in patients with known BRCA mutation, see text
ER negative and HER2-positive		
T1a node negative	No systemic therapy	
T1 b,c node negative	Chemotherapy plus trastuzumab	Consider paclitaxel plus 12 months trastuzumab without anthracycline
Higher T or N stage	Anthracycline → taxane with concurrent trastuzumab continued to 12 months	Patients unsuitable for anthracycline may be treated with TCH regimen, though cardiac contraindications to anthracycline may also argue against trastuzumab [115]
ER positive and HER2-positive	As above plus endocrine therapy appropriate to menopausal status as below	
ER positive and HER2-negative (luminal disease)		
Without markers of less endocrine responsiveness (luminal A-like)	Endocrine therapy alone according to menopausal status	See Table 2. Consider chemotherapy if four or more nodes involved
Premenopausal low risk	Tamoxifen 5 years	
Premenopausal other	Tamoxifen 5–10 years or OFS plus tamoxifen or OFS plus exemestane	See criteria in papers [3, 4, 116]
Postmenopausal low risk	Tamoxifen 5 years	
Postmenopausal other	AI preferably up front; extended adjuvant therapy (see text)	No evidence on the safety or efficacy of more than 5 years of an AI
With markers suggesting lesser endocrine responsiveness (luminal B-like)	Endocrine therapy as above plus adjuvant cytotoxic chemotherapy in many cases	See Table 2
Factors supporting omission of cytotoxic chemotherapy despite 'luminal B-like' phenotype		'good' result of multiparameter molecular test if available

therapy for a total of 10 years using either further tamoxifen or, if the patient is clearly postmenopausal, an AI.

For patients postmenopausal at presentation, tamoxifen alone may be suitable for those at lower risk while, for other patients, an AI should be considered and given up front, especially in those at higher risk.

Many patients now receive an AI for all or part of their first 5 years of endocrine therapy. While there is less evidence to guide extended endocrine therapy in such patients, continuation of an AI to a cumulative exposure of 5 years seems appropriate. There is no evidence about the safety or efficacy of longer periods of AI therapy, but studies of such treatment are in progress.

acknowledgements

We gratefully acknowledge all participants in the 14th St Gallen conference for their many useful suggestions. In addition to Panel members, we thank Sabina Briner, Carmen Criscitiello, and Shari Gelber for their substantial assistance in the preparation of this report.

funding

Support for the conference was provided by the Educative Foundation, St Gallen Oncology Conferences (SONK) from registration fees paid by the conference attendees; by Grant No. CA75362 from the United States National Cancer Institute (IBCSG Statistical Center, M. Regan, PI) and by Susan G. Komen® (grant No SPP150019).

disclosure

Conflict of interest statements from all presenters and Panel members were available on-line during the conference and are listed in supplementary Appendix S1, available at *Annals of Oncology* online.

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appendix

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