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Zurich Consensus: Statement of German Experts on St. Gallen Conference 2011 on Primary Breast Cancer (Zurich 2011)

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Summary
Every 2 years, the International Consensus Conference on the Treatment of Primary Breast Cancer takes place in St. Gallen. Given that the concept of the St. Gallen Consensus Conference mainly reflects an international opinion, it appears useful to adapt the results of the vote for everyday therapy in Germany. A German working group comprising 28 breast cancer experts, amongst whom there are 3 members of the international St. Gallen panel, has therefore commented on this year's St. Gallen Consensus Conference (2011) from the German viewpoint. The focus of interest of this year's St. Gallen Conference was tumour biology as the starting point for decisions regarding individual therapy. There was an intensive discussion in relation to the clinical relevance of predictive and prognostic factors and possible consequences for decisions regarding therapy. Therefore, questions concerning the indication for adjuvant chemotherapy focused especially on the significance of the molecular phenotype of the tumour. In addition, important points for discussion were also the value of complete axillary dissection and the use of accelerated complete breast irradiation.

Zusammenfassung
Alle 2 Jahre findet in St.-Gallen die internationale Konsensuskonferenz zur Behandlung des primären Mammakarzinoms statt. Vor dem Hintergrund, dass das Konzept der St.-Gallen-Konsensuskonferenz vor allem ein internationales Meinungsbild widerspiegelt, erscheint es sinnvoll, die Abstimmungsergebnisse für den Therapiealltag in Deutschland zu adaptieren. Eine deutsche Arbeitsgruppe von 28 Brustkrebsexperten, darunter 3 Mitglieder des internationalen St. Gallen-Panels, hat daher die Abstimmungsergebnisse der diesjährigen St.-Gallen-Konsensuskonferenz (2011) aus deutscher Sicht kommentiert. Inhaltlicher Schwerpunkt der diesjährigen St.-Gallen-Konferenz war die Tumorbiologie als Ausgangspunkt für die individuelle Therapieentscheidung. Intensiver Diskussionsbedarf bestand bei der klinischen Relevanz prädiktiver und prognostischer Faktoren und den möglichen Konsequenzen für die Therapieentscheidung. So fokussierten insbesondere die Fragen zur Indikation einer adjuvanten Chemotherapie auf die Bedeutung des molekularen Phänotyps des Tumors. Wichtige Diskussionspunkte waren darüber hinaus der Stellenwert der kompletten Axilladissektion und der Einsatz der beschleunigten Gesamt-Brust-Bestrahlung.

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Introduction

The St. Gallen Consensus Conference on the Diagnosis and Treatment of Primary Breast Cancer has worldwide importance. The panel of this year's 12th St. Gallen Consensus Conference (March 16–19, 2011) comprises 51 experts from 19 countries, including 4 representatives from Germany. The recommendations of the conference are based on the vote of panellists who represent different specialities and different countries from all continents of the world with very different health systems and resources. This framework justifies the consensus essentially reflecting the opinion of these experts, although published evidence-based data are the basis for individual decisions. It appears appropriate to comment on the results of the voting at the conference from a German perspective. A German working group consisting of 28 breast cancer experts therefore interpreted the results of the votes in St. Gallen related to everyday clinical practice in Germany. Because of country-specific differences, not all of the questions raised for voting in St. Gallen have equal clinical relevance for the therapeutic situation in Germany.

The focus of this year's St. Gallen Consensus Conference was tumour biology and the questions of influence of phenotype of the tumour on individual therapy decisions. The basis are the subtypes illustrated in table 1 which, in keeping with current knowledge, are associated with different tumour biology and a different disease course. In addition, surgical treatment, radiation therapy and systemic treatment were discussed. The questions raised for voting were answered by the panellists with 'yes' (agreed) or 'no' (rejected) or 'abstain/do not know'.

The German group drew attention to two points: i) With increasing importance of tumour biology or phenotyping of the tumour, histopathology has gained importance. Validated and standardised quality assurance concepts in pathology are more important than ever; ii) Participation in controlled clinical studies has a high value and should be further pursued. This also applies to numerous therapeutic questions, which were addressed in St. Gallen. However, individual studies will only be cited in exceptions.

Prognostic and Predictive Factors

Characterising Phenotypes

In response to the question of whether the various subtypes of breast cancer can be defined exclusively – that is without the use of a multi-gene assay – on the basis of immunohistology utilizing currently available and reproducible pathology parameters, such as hormone receptor status, HER2 status, grading and Ki-67, a clear majority of panellists in St. Gallen responded with 'yes'. The German working group agrees, but notes that the proliferation factor Ki-67 has not been a standard marker until now, however, it can be of value in some cases – in accordance with the AGO recommendation 2011. Apart from methodological problems in the measurement of Ki-67, the cut-off values have still not been unambiguously defined. It is accepted that a Ki-67 value of ≤ 10% measured using immunohistochemical techniques shows a low proliferation rate and is associated with a good prognosis. Ki-67 determination is therefore suitable, for example in order to better differentiate between luminal A (Ki-67 ≤ 10%) and luminal B type. What remains unclear is the cut-off value for high proliferation. Hence, there still is a lack of data from prospective randomized studies, as well as a standardized determination of Ki-67.

Accordingly, the St. Gallen panellists and the German experts agree that hormone receptor expression (oestrogen receptor (ER)+/progesterone receptor (PgR)–) and/or a high level of Ki-67 expression and/or G3 grading, as well as HER2 positivity are the best available markers to differentiate luminal B from luminal A type. The luminal A type can be defined by a clear positive ER and PgR status (ER+/PgR+), the absence of HER2 overexpression and a low Ki-67 value. The German experts drew attention, however, to the fact that currently no therapeutic consequences can be directly concluded on the basis of the typing as luminal A or B alone. The St. Gallen panellists confirmed this in a later vote on the clinical value of molecular gene expression analyses. The marker for the definition of a carcinoma of the breast of the basal type (basal-like), cytokeratin 5 and 6 (CK5/6), and/or epidermal growth factor receptor (EGFR) expression, have not yet been validated in clinical routine.

Table 1. Overview of currently relevant molecular subtypes of breast cancer; subtypes defined on the basis of gene expression are frequently not exclusively associated with the specified marker profile

Basal-like BRCA	Basal-like, sporadic	HER2 +	Luminal B	Luminal A
ER–/PgR–	ER–/PgR–	ER–/PgR–	ER+/PgR–	ER+/PgR+
G3	G3	G3	G1,2	G1
Ki-67 50–60%	Ki-67 50–60%	Ki-67 40–50%	Ki-67 5–20%	Ki-67 5%
HER2–/EGFR+	HER2–/EGFR+	HER2+	HER2–	HER2–
BRCA1/2+	BRCA1/2–			
P53/cMYC↑	P53/cMYC↑			

ER = Oestrogen receptor; PgR = progesterone receptor; EGFR = epidermal growth factor receptor.

HER2 Overexpression

In order to define HER2 positivity, 68% of the St. Gallen panellists voted for maintaining the FDA definition: accordingly, more than 10% of the tumour cells must be immunohistochemically positive or in fluorescence in situ hybridisation (FISH) there must be a HER2 gene/centromere 17 ratio greater than 2.0. The FDA definition is based on the inclusion criterion of adjuvant trastuzumab studies in patients with HER2-positive breast cancer. The German working group recommended to use the AGO recommendation (2011) or the ASCO/CAP guidelines (2007) as an orientation. Accordingly, HER2-positivity is defined as ≥ 30% immunohistochemically detected HER2-positive tumour cells (IHC3+) or a FISH ratio ≥ 2.2. In the case of a HER2 expression > 10 to < 30% (IHC2+), a FISH (or CISH) analysis is additionally recommended.

Molecular Gene Expression Analysis

The German experts agreed with the majority of the St. Gallen panellists that the decision regarding therapy should not be made on the basis of a molecular gene expression analysis and the tumour subtype defined in relation to this. They drew attention to the fact that an intrinsic tumour type is not a standardised predictive factor and that allocation to a particular tumour type on the basis of a gene expression profile is not qualified for the indication of a particular adjuvant systemic therapy. This is also not a predictor for response to a particular chemotherapy regimen or specific cytostatics. With this opinion, the St. Gallen panellists and the German experts confirmed that currently, as a rule, the phenotype can be determined with a sufficient degree of certainty in everyday clinical practice by non-genetic tests such as, for example, grading, hormone receptor status and HER2 status, as well as optionally Ki-67 determination.

In contrast to the situation 2 years ago, the 2 molecular tests Oncotype DX® (Genomic Health Inc., Redwood City, CA, USA) and Mammaprint® (Agendia, Amsterdam, The Netherlands) were evaluated differently by the panellists, although no new study data have become available. While a clear majority (84%) of panellists voted for Oncotype DX to be used (where available) in patients with hormone-sensitive breast cancer in order to predict the response to CMF chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil), the majority of panellists (64%) rejected the use of Mammaprint in this context. The St. Gallen panel adopted no position regarding the questions in which patients or how frequently such an additional determination is necessary.

The differing vote of the St. Gallen panellists is debatable since comparable data are available for both test systems. The German experts explain the different evaluations by logistic problems, as Mammaprint is performed on fresh tissue. The positive vote for Oncotype DX was discussed by the German experts as a matter of controversy because for both tests only data from retrospective studies are available. From the German perspective, participation in ongoing studies is recommended as long as no prospective data are available. Oncotype DX should be used outside clinical studies only in individual cases in addition to the clinical and histopathological parameters. The test can be helpful, for example in patients with positive hormone receptor and negative HER2 status and only 1–3 affected lymph nodes (pN0, pN1a). Here, retrospective data show that patients with a low recurrence score (applies only to pN0 and pN1a) or a low and intermediate recurrence score (applies only to pN0) have no significant advantage from adjuvant chemotherapy [1, 2]. Both tests are not covered by medical insurance.

uPA/PAI-1 Determination

The determination of uPA/PAI-1 as a predictive factor for or against the use of chemotherapy was rejected in St. Gallen by the majority of panellists (50%) with 23% positive votes and 27% abstentions. The German experts did not agree with this statement. Based on the available data (LOE 1a) uPA/PAI-1 are valid standardised and evidence-based prognostic and predictive factors for patients with node-negative breast cancer and intermediate risk profiles (e.g. pN0 G2), which is substantiated by prospective data. This is also in accordance with the AGO recommendation 2011. uPA/PAI-1 must be determined from fresh tissue.

Local Therapy

Axillary Dissection

The focus of the voting on locoregional therapy were the value of complete axillary dissection and the type of local breast irradiation. There was no voting on surgery of the breast.

With a clear majority (71%), the St. Gallen panellists rejected immunohistochemical assessment of sentinel lymph nodes (SLN) as a routine procedure. More than 90% of panellists considered exclusive immunohistochemical detection of isolated tumour cell clusters (ITC or pN0(i+)) not to be an indication for complete axillary dissection, independent of whether the patients have a mastectomy or breast-conserving operation. The German experts agree and reinforce the fact that immunohistochemical assessment of the SLN has no clinical significance.

For patients with a breast-conserving operation, the St. Gallen panellists, in contrast to the vote taken 2 years ago, viewed neither the evidence of ITCs nor micrometastases (pN1mi) in the SLN as an indication for a complete axillary dissection. It has been criticised that the definitions of ITC and micrometastases used in the questions in St. Gallen did not correspond to the international UICC classification. However, as the majority of panellists rejected a complete axillary dissection up to a focal size of 2 mm (= upper cut-off for micrometastases) in the SLN, the result of the vote is essentially

clear: following a breast-conserving operation, in the case of a clinically and sonographically normal axilla, despite evidence of ITC or micrometastases in the SLN, complete axillary dissection is not recommended.

The German experts agree with this statement, in conformity with the current AGO recommendation (fig. 1), and state their view accordingly: a complete axillary dissection can be omitted when the following conditions are present: clinically and sonographically normal axillary lymph node status (cN0), ≤ 2 tumour-infiltrated SLN, breast-conserving operation, cT1/2, tangential radiation field of the breast, and adequate adjuvant systemic therapy. The German experts emphasised that these patients must be informed about the data situation. An extra-radiation therapy field of the axilla is not indicated [3]. In the case of patients who have undergone a mastectomy and who have a positive SLN biopsy, there is still an indication for axillary lymphadenectomy. The working group also mentioned that internationally validated definitions of isolated tumour cell clusters and micrometastases should be respected. The procedure to be followed in the case of macrometastases in the SLN was only voted on in St. Gallen in relation to patients who had undergone mastectomy. In this case, in the concurring view of the St. Gallen panellists (> 70%) and the German experts, a complete axillary dissection should (still) be performed.

Radiation Therapy Following Breast-Conserving Operations

With a clear majority (68%), the panellists in St. Gallen confirmed radiation therapy as a standard following a breast-conserving operation for patients with R0-resected ductal carcinoma in situ (DCIS). The German experts agreed with this opinion. Postoperative irradiation reduces the local relapse risk by more than half. In the case of older DCIS patients (≥ 70 years), the majority of panellists voted that irradiation

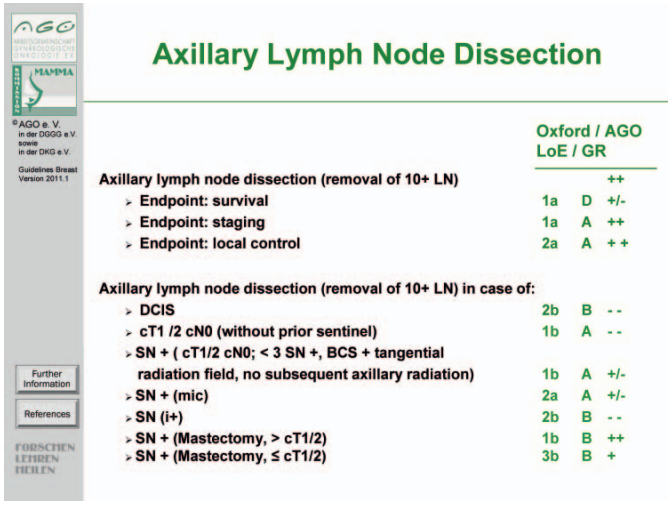

Fig. 1. AGO recommendation regarding axillary lymph node dissection (*www.ago-online.de*).

can be omitted. The German working group agreed, and pointed out that this shouldtake into account benefits and side effects. A majority of the St. Gallen panellists voted that in low-grade DCIS postoperative radiation can be omitted. The German experts were against this vote and recommended an individual side effect/benefit assessment with the limitation that low-risk patients cannot always be unambiguously identified.

In relation to the type of radiation for an invasive carcinoma, the panellists considered accelerated whole breast radiation therapy (WBRT) with a clear majority (92%) to be an acceptable option. The German working group agreed, but stated that accelerated WBRT should be limited to particular clinical situations [4]. An advantage of accelerated WBRT is the clearly shortened duration of therapy from 6 weeks to 16 days.

There was no unity in the results of voting in St. Gallen with regard to the question of whether standard irradiation of the breast should be preferentially used in patients with invasive breast cancer and extended vascular invasion. The controversial results of voting make clear that, at present, there are no prospective data with regard to this question. The German experts therefore expressed the opinion that this should be decided in the individual case, taking into account the overall clinical situation and weighing up the individual side effect/benefit situation.

The majority of the St. Gallen panellists (49 vs. 36%) voted for intra-operative partial breast radiation therapy (PBRT) following a breast-conserving operation as a definitive radiation therapy to be sufficient so that no external radiation (boost, complete breast radiation) is necessary. The German experts discussed this point controversially. Because of the low event rate (local relapse) and the relatively short post-observation period, no general recommendation can be made for PBRT. Further study results must be awaited. Participation in the studies, for example in the Targit studies, is recommended. There is unity that intra-operative PBRT in the case of breast-conserving operations is an acceptable alternative to external boost-radiation of the tumour bed. In addition, the St. Gallen panellists viewed (intra-operative) PBRT as an option for older patients (> 70 years). The German experts agree with this as a 'can' option for individual cases. The St. Gallen view of whether (intra-operative) PBRT is also an option for patients who, because of an earlier lymphoma disease, have received total nodal irradiation was controversial. The German experts recommend discussing this with the patient and colleagues who are specialists in radiation therapy. A second radiation therapy is not fundamentally excluded.

Radiation Therapy Following Mastectomy

There is agreement that adjuvant radiation for patients with 4 and more affected lymph nodes, who have undergone mastectomy, is standard. No general recommendation was

given by the St. Gallen panellists with regard to postoperative radiation for patients who have undergone mastectomy with 1–3 affected lymph nodes, as well as for those without lymph node involvement and ≥ pT2 tumours. In accordance with the AGO recommendation 2011, the German experts recommend, in the case of 1–3 involved lymph nodes, to make the indication dependent on the age of the patient and other risk factors (LOE 1a GR+). The voting results with regard to young patients (< 45 years) or those with extended vascular invasion (lymph- or haemangiosis carcinomatosa, i.e. L1 and/or V1) and/or 1–3 involved lymph nodes was clearly more heterogeneous. With a narrow majority, in both situations, routine postoperative radiation following mastectomy was recommended. In the opinion of the German experts, the clinical situations described are 'can' criteria. Because of the lack of clinical data, the indication for postoperative radiation should be performed on an individual basis in these cases (cf. AGO recommendation 2011).

Adjuvant Antihormonal Treatment

Premenopausal Patients

A hormone-sensitive breast cancer is defined by ≥ 1% of the tumour cells with ER+ and/or PgR+. For a premenopausal patient with hormone-sensitive cancer, both treatment with tamoxifen (± chemotherapy), as well as a combination of tamoxifen plus ovarian function suppression (OFS) are possible. The combination of tamoxifen plus OFS (luteinizing hormone-releasing hormone (LHRH) agonist) is, however, not superior to the administration of tamoxifen alone (± chemotherapy). In this case, the German working group agreed for the given situation with the majority of the St. Gallen panellists. The German experts substantiated their view by noting that, on the basis of the available data, treatment with tamoxifen alone was sufficient, independent of whether therapy-induced amenorrhoea is present or not. The combination of tamoxifen plus OFS following adjuvant chemotherapy is, if at all, an option for young patients under 40 years of age. The question of whether patients would actually benefit from the additional administration of a LHRH analogue will be shown by the SOFT and TEXT studies.

More than 70% of the St. Gallen panellists consider OFS alone to be a therapy option for premenopausal patients when there are contraindications against tamoxifen. From the German perspective, the only use of OFS as an alternative to tamoxifen is, for example, in women with a clinically relevant contraindication to tamoxifen such as thrombosis or embolism.

The question of whether OFS alone is also an alternative following prior adjuvant chemotherapy was viewed controversially. When no other anti-hormonal therapy is available, there was a majority agreement and reference was made to the uncertain data situation. Attention should be drawn to the fact that the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group [5] for patients following adjuvant chemotherapy has shown no effect of an OFS. In contrast to the St. Gallen panellists, the German experts view the combination of OFS plus aromatase inhibitor not to be an alternative. There was a controversial discussion amongst the German experts concerning the question of whether, in view of the spectrum of side effects, the combination of tamoxifen with anticoagulation is an option.

Postmenopausal Patients

A change was seen in the results of voting compared with St. Gallen 2009 with regard to the value of aromatase inhibitors (AI) in postmenopausal patients with hormone-sensitive early carcinoma of the breast. In response to the question of whether fundamentally all postmenopausal patients must receive an AI in the course of anti-hormonal treatment, only 50% voted yes. From the German perspective, most postmenopausal women should receive an AI for at least 2–3 years (cf. AGO recommendation 2011). A clear majority of panellists (79%) voted in favour of postmenopausal patients with affected lymph nodes in general receiving an AI. The German experts agreed with this statement.

Nonetheless, the St. Gallen panellists voted with a clear majority that the only administration of tamoxifen is still, as previously, an option. From the German perspective, an indication for the administration of tamoxifen can exist, for example, in the case of older patients, in the event of intolerance to AI, with severe osteoporosis, or when there is a low risk of relapse (small tumour, pN0, G1). In a later question, 98% of the St. Gallen panellists view tamoxifen to be an alternative in the case of intolerability to an AI. The German experts agree with this statement.

If an AI is indicated, 52% of the St. Gallen panellists would not give it upfront. The German working group commented that there are valid study data for both upfront use and also the sequential administration of AI before or after tamoxifen, so that all 3 options are possible in everyday clinical practice.

There is agreement that AI should not be given for longer than 5 years. Also, in the case of patients with involved lymph nodes, the majority of panellists (55%) rejected long-term therapy with AI. The German experts agreed, as there are no data available from controlled clinical studies that justify the use of AI for more than 5 years, and recommend to participate in studies such as the SOLE study *(www.germanbreastgroup.de)*. In the case of pre- and perimenopausal patients, AI are not indicated.

The Significance of CYP2D6 Determination and the HER2 Receptor

There was agreement that CYP2D6 determination has no relevance for the decision of whether postmenopausal patients should receive an AI or tamoxifen. Data regarding CYP2D6 determination in the case of premenopausal patients

Untch/Gerber/Möbus/Schneeweiss/Thomssen/
von Minckwitz/Beckmann/Blohmer/Costa/
Diedrich/Diel/Eiermann/Friese/Harbeck/
Hilfrich/Jackisch/Janni/Jänicke/Jonat/Kaufmann/
Kiechle/Köhler/Kreienberg/Maass/Marschner/
Nitz/Scharl/Wallwiener

are not available. The German experts recommend patients to participate in the register study in Tübingen.

The question whether the therapy decision for or against AI or tamoxifen should be made dependent on biological tumour variables was voted controversially. From the German viewpoint, this corresponds to the clinical reality, as prospective data from controlled clinical studies are lacking. As a rule, postmenopausal patients with hormone-sensitive carcinomas of the breast and an increased risk profile receive an AI.

The German experts agreed with the St. Gallen panellists that patients with hormone-sensitive and, at the same time, HER2-overexpression additionally need chemotherapy. In postmenopausal patients, HER2 overexpression should have no influence on the subsequent decision regarding endocrine therapy. At present, there are no validated study data available that indicate that patients benefit more from AI than from tamoxifen. There is also agreement that overweight is not a contraindication to AI. The German experts pointed out that the data relevant to this question are contradictory.

The Adjuvant Use of Bisphosphonates

The adjuvant use of bisphosphonates has again become the subject of discussion as a result of the AZURE data. Nonetheless, the German experts emphasise the fact that patients can benefit from the use of bisphosphonates independent of their menopausal status and other adjuvant therapy. For the majority of patients additional adjuvant treatment with a bisphosphonate reduces the probability of a relapse, which in some studies was also reflected in a lower rate of mortality. It is currently postulated that, in particular, oestrogen-deficient patients (i.e. with an activated bone metabolism) appear to benefit from the administration of adjuvant bisphosphonates. These are, for example, patients who have been postmenopausal for more than 5 years.

The questions raised for voting in St. Gallen focussed on the bisphosphonate zoledronate. The question of whether premenopausal patients should, in addition to adjuvant endocrine therapy with or without OFS, receive zoledronate was rejected by the majority (81%) of the St. Gallen panellists. The German experts are in agreement but pointed out that an oncologic advantage for the additional administration of bisphosphonates in patients without adjuvant chemotherapy has been validated. The St. Gallen panellists also rejected the additional administration of zoledronate for postmenopausal patients. The German experts do not agree with this second vote referring to the clinical data evidence. The AGO guideline 2011 gives a clear recommendation in this context for postmenopausal patients (zoledronate).

In 2 further votes, the St. Gallen panellists rejected the proposition that zoledronate – given every 6 months in addition to adjuvant endocrine therapy – improves the disease-free survival. For patients who have been postmenopausal for some years, 44% of the panellists still rejected this, with 23% abstentions. Both votes were rejected by the German experts who mentioned the positive clinical data situation. There is currently no adjuvant indication for the RANK ligand denosumab. Study data justifying the substitution of zoledronate by denosumab in the adjuvant situation are not available.

Adjuvant Chemotherapy

Chemotherapy in Patients with Positive Hormone Receptor Status

The focus of consideration with regard to adjuvant chemotherapy in St. Gallen was the influence of conventional risk factors and biological variables on the decision for therapy. According to the St. Gallen meeting, independent of the nodal status, reasons for adjuvant chemotherapy are grading (G3 tumour), increased Ki-67 values (> 14%), low hormone receptor expression (< 50%), positive HER2 status and invasive ductal triple-negative carcinoma of the breast (TNBC: ER–, PgR–, HER2–). Of note, special histological forms such as adenoid cystic cancer, metaplastic and medullary cancer are also negative for all 3 receptors, but do, however, show a good prognosis. These special forms are not allocated to the TNBC.

The German experts comment that grading in clinical studies is one of the most siginificant prognostic and predictive factors. The proliferation factor Ki-67 can, especially in the case of hormone receptor-positive tumours, be an additional criterion for adjuvant chemotherapy (distinguishing between luminal A and B tumours). Problematic are – as already discussed – the heterogeneous Ki-67 tests and heterogeneous cut-off value for high proliferation.

The cut-off value used in St. Gallen for a low hormone receptor expression of < 50% is, from the German point of view, arbitrary. There are no prospective data available regarding this point. Basically, the following rule applies: the lower the hormone receptor expression, the greater is the efficacy of chemotherapy. From the German perspective, evidence of HER2 overexpression in pT1b tumours is, independent of the nodal status, an indication for chemotherapy. This is true independent of ER status (cf. AGO/NCCN recommendation). Also, the presence of a TNBC implies a clear indication for chemotherapy. However, the German experts stated that there are no data available for benefit of adjuvant chemotherapy in TNBC < 1 cm. In this case, the decision regarding therapy should be based on additional factors, such as the age of the patient, grading, or proliferation factor.

Controversial: Nodal Status

Lymph node status per se as an indicator for the additional use of chemotherapy was rejected by 60% of the St. Gallen panellists. The voting was viewed controversially by the German experts. Lymph node status still remains the strongest prognostic parameter, but is, however, not a good predictive

factor. A positive nodal status implies an increased risk, but does not result automatically in an indication for adjuvant chemotherapy. The problem in everyday clinical routine is in the case of patients with 1–3 involved lymph nodes (medium risk) following complete axillary dissection, who have an excellent outcome with a 5-year survival rate of 95% with adequate anthracycline/taxane-containing chemotherapy (WSG/AGO study [6]). However, there is also the danger of overtreatment. The German experts see the need of identifying a subgroup in patients with 1–3 affected lymph nodes that does not need chemotherapy. Possibly, in this case, optimised prognostic and predictive factors such as gene expression analyses will bring greater clarity in the future. At present, one should focus on the age of the patient and the tumour biology. There is agreement that ≥ 3 involved lymph nodes following complete axillary dissection represent a clear indication for chemotherapy.

Lymphovascular Invasion

There are no prospective data available regarding the value of lymphovascular invasion as a criterion for the use of chemotherapy. The general opinion is equally controversial. From the German point of view, lymphovascular invasion can be of value in individual cases for the use of chemotherapy, for example, N0 patients.

Gene Expression Analyses

Since St. Gallen 2009, the retrospective data situation regarding the value of gene expression analyses using Oncotype DX and Mammaprint for chemotherapy decision in the case of patients with hormone receptor-positive cancer, has been extended. This also includes, for example, patients with 1–3 involved lymph nodes. The German experts agreed with this year's vote of the St. Gallen panellists that both genetic tests could be of value in addition to classical parameters. Once more, the German experts emphasized that a general recommendation outside clinical studies is not justified as, up until now, no data from prospective studies are available.

The Influence of the Phenotype on the Therapy Decision

In St. Gallen, numerous votes related to the phenotype (table 1) on the chemotherapy decision. From the German point of view, only a few retrospective analyses and no prospective data are available and phenotype itself is not a predictor for a particular chemotherapy. Luminal A cancer includes classic endocrine-sensitive tumours. The St. Gallen panellists and the German experts agreed that this phenotype probably requires no chemotherapy. The therapy of choice for patients with luminal A tumours is endocrine treatment. For luminal A patients, there is no preferred chemotherapy regimen, should it be indicated in rare cases.

Hormone receptor-positive patients with luminal B cancer have an increased risk of relapse and are considered to be chemotherapy-sensitive because of the increased rate of proliferation. As a rule, they receive chemotherapy followed by endocrine treatment. The St. Gallen panellists voted in favour of giving these patients an anthracycline-containing and taxane-containing regimen. There is agreement from the German experts. From retrospective analyses, taxane-/anthracycline-containing regimens are superior to anthracycline-containing therapy alone. The rare case of a luminal B tumour with HER2 overexpression requires chemotherapy with trastuzumab.

Basal-like cancer has an unfavourable tumour biology. The St. Gallen panellists also voted in favour of treating these patients with an anthracycline-/taxane-containing chemotherapy. The German experts commented that the regimen used should contain anthracyclines and taxanes.

The proposal to treat patients with invasive ductal TNBC with a dose-dense chemotherapy was approved by a majority (52%) in St. Gallen. At present, only few subgroup data relating to this point are available. Advantages for patients with TNBC have for example been demonstrated in a dose-dense therapy study from Germany [7]. No indication exists in patients with invasive ductal TNBC for an antiangiogenic therapy in addition to chemotherapy. Likewise, there are no prospective data available regarding the use of platinum compounds in ductal invasive TNBC.

Neoadjuvant Chemotherapy

The neoadjuvant therapy concept was further developed and validated, especially in Germany, in the context of large prospective clinical studies. It is now well established and internationally accepted for the treatment of patients with early breast cancer. German study data have been cited in numerous lectures at international congresses. The focus of attention in neoadjuvant therapy in St. Gallen was on establishing the indication and the choice of drugs. In contrast to the questions raised in relation to adjuvant therapy, tumour biology received hardly any consideration.

Indication for Neoadjuvant Therapy

In the view of the majority (60%) of the St. Gallen panellists, the main aim of neoadjuvant therapy is the improvement of surgical options, especially increasing the rate of breast-conserving operations. The German experts agreed, but drew attention to other goals. The response associated with the neoadjuvant concept enables early individual proof of the value of a therapy and therefore contributes to a greater individualisation of treatment and the early introduction of new therapy concepts. Moreover, neoadjuvant therapy facilitates the evaluation of response and outcome. The achievement of a pathologically complete remission (pCR) in HER2-positive tumours and TNBC is considered to be a strong predictive marker for long survival. The German experts and St. Gallen panellists agreed that a neoadjuvant therapy should be used

with the highest chance of response (cf. AGO recommendation 2011).

Similar to the adjuvant situation, neoadjuvant chemotherapy is less effective in patients with a low risk profile, for example, a tumour with a low proliferation rate. Overall, 64% of the panellists in St. Gallen confirmed this. A low proliferation rate is to be assumed, for example, with a low Ki-67 value. For the decision of whether neoadjuvant chemotherapy or an endocrine therapy is indicated, the German working group recommended an orientation based on the phenotype of the tumour, which implies the proliferation behaviour. Correspondingly, patients with a luminal A breast cancer can also receive neoadjuvant and endocrine therapy. Overtreatment should, however, be avoided.

A total of 77% of the St. Gallen panellists rejected the use of neoadjuvant chemotherapy in the case of patients with highly endocrine-sensitive carcinoma of the breast, such as (pure) lobular carcinoma. The German working group agreed with this. The German experts noted that pure lobular carcinomas, which are highly endocrine-sensitive, show favourable grading (G1/2) and are HER2-negative; hence, they most likely do not benefit from neoadjuvant therapy.

Substance Selection for Neoadjuvant Chemotherapy

In the choice of substance, the overwhelming majority of panellists in St. Gallen (82%) voted for neoadjuvant chemotherapy favouring the use of anthracycline-containing and taxane-containing regimens. Compared to the voting from 2 years ago, the acceptance of taxanes has increased by 20%. The German working group also interpreted this to be an indication of the good acceptance of the results of the German study. With a large majority (86%), the panellists in St. Gallen voted in favour of using an adjuvant standard chemotherapy regimen also in the neoadjuvant setting. In Germany, this has been recommended since 2006 in the AGO recommendation and the S3 guideline.

Therapy of HER2 Overexpressing Breast Cancer

With HER2 overexpression, an anti-HER2 therapy is always indicated in addition to neoadjuvant chemotherapy. Overall, 87% of the panellists in St. Gallen confirmed this. The German experts agreed with the comment that the chemotherapy should be anthracycline-/taxane-containing. The German experts had a strong debate as to whether trastuzumab should be used simultaneously with anthracycline or at the beginning of the taxane-containing therapy. Prospective study data are available for both options. The minimal consensus of the German experts is that the decision should be made using the cardiac risk profile of the patient. In the case of simultaneous administration of anthracycline, before and during treatment, regular cardiac monitoring should be carried out.

The German experts agreed with the St. Gallen panellists that the dual HER2 blockade is currently still not a validated therapy option in a neoadjuvant setting for the treatment of patients with HER2-positive tumours. The pathologic complete remission of 40–50% in these patients correlates with an excellent outcome [10]. The use of this therapy approach in clinical studies is recommended.

Neoadjuvant Endocrine Therapy

There is agreement that neoadjuvant endocrine therapy alone with highly hormone-sensitive tumours is fundamentally possible. It is still unclear how long the therapy should go on for. This is also reflected in the results of voting: 15% voted for 3–4 months, 39% for 4–8 months, and 46% until the best therapy response has been achieved. In contrast, the German working group commented, contrary to the majority of panellists in St. Gallen, that the best therapy results are achieved with a 4-month AI therapy. The duration of therapy is controversially discussed.

HER2-Positive Breast Cancer

The German experts pointed out that quality-assured HER2 testing is an indispensable prerequisite for anti-HER2 therapy. The participation in validated quality controls and the application of ASCO/CAP guidelines is recommended.

A preference for a particular chemotherapy regimen for treating a HER2-positive early breast cancer was rejected by the majority of St. Gallen panellists. The German experts agreed, but noted that anthracycline- and taxane-containing chemotherapy regimens, independent of the nodal status of the patient, are standard for the treatment of HER2-positive early breast cancer. The St. Gallen panel confirmed this: 98% of the panellists supported the view that chemotherapy should contain an anthracycline, 75% of the panellists judged this to be essential, and 83% supported the use of a taxane as obligatory. In addition to this, the German working group also saw the anthracycline-free TCbH regimen (docetaxel, carboplatinum, trastuzumab) as a valid therapy option in the case of patients with an anthracycline contraindication [8].

All panellists (100%) voted for trastuzumab for 1 year as (neo)adjuvant chemotherapy in patients with HER2-overexpression. The German experts agreed without reservations. A clear majority of the St. Gallen panellists (79%) also approved this for patients with HER2-positive breast cancer between 5 mm and 1 cm and pN0. From the German point of view, this applies without restriction in the case of patients with positive nodal status, and should be taken into consideration for pN0 patients in accordance with the AGO guideline 2011 and the NCCN guidelines.

There is also agreement that trastuzumab is only indicated together with chemotherapy. The St. Gallen panellists especially considered the simultaneous and optional as well as the sequential administration of trastuzumab as a valid option in

addition to chemotherapy. The majority of the German experts agreed with this opinion, but mentioned the potentially increased cardiac side effects with the simultaneous administration of trastuzumab and anthracyclines, which can be diminished by sequential application or the use of TCbH.

There are currently no data available concerning the question of whether to use trastuzumab for less than or more than 1 year. Corresponding prospective clinical studies (6 vs. 12 months or 12 vs. 24 months) are still in progress or in the stage of evaluation. There is therefore agreement that a shorter or longer duration is currently not an option in everyday clinical practice. Only for countries with limited resources, the majority of St. Gallen panellists (71%) admit that administration of trastuzumab over a shorter period of time (< 1 year) is possible, in order to prevent a situation in which trastuzumab will be withheld from patients with HER2-positive tumours. Following a debate, the German experts agree but mentioned that this is not evidence-based and has no validity for Germany. The standard is to give trastuzumab for 1 year in accordance with the available data and licensing for the substance.

There is also no indication for the use of trastuzumab alone ± endocrine therapy. However, the St. Gallen panellists voted in favour of this being an option for patients with contraindications to chemotherapy. The German working group rejects this statement. The recommendation is – whenever possible – to use the synergy between trastuzumab and chemotherapy.

Male Breast Cancer

In rare cases, men also develop breast cancer (about 400–500 new cases each year in Germany). The standard endocrine therapy is tamoxifen. An indication for AI does not exist for men. The German working group mentions the study to be started in the near future called MALE study *(www.germanbreastgroup.de),* in which the use of AI will be investigated.

Disclosure Statement

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