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Review

Guidelines for the adjuvant treatment of postmenopausal women with endocrine-responsive breast cancer: Past, present and future recommendations

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ABSTRACT

Treatment guidelines are useful tools that enable physicians to integrate the latest clinical research into their practices. The large volume of rapidly evolving clinical data in breast cancer has been summarised and incorporated into treatment recommendations by well-known and reliable institutions, including the National Comprehensive Cancer Network, the American Society for Clinical Oncology, the European Society for Medical Oncology and the St. Gallen International Consensus Panel. Adjuvant therapy is a key component of breast cancer treatment, and many of the current consensus guidelines now recognise the important role of the aromatase inhibitors as an alternative to or in sequence after tamoxifen, hitherto the standard adjuvant treatment of choice for receptor-positive women. Data from ongoing trials such as the Breast International Group 1–98 trial and those still in the accrual phase will be forthcoming and will likely result in a further refinement of treatment recommendations over the course of the next few years. Despite the availability of such guidelines, however, there is evidence that adherence to and implementation of treatment recommendations is less than optimal. Further research is needed to determine more effective means of disseminating those clinical recommendations that can have a significant impact on treatment strategies and ultimately improve outcomes in breast cancer.

1. Introduction

Recent advances in the treatment of breast cancer have greatly increased the range of therapeutic options for patients. The emergence of the third-generation aromatase inhibitor (AI) drugs as effective and well-tolerated potential alternatives to tamoxifen in the adjuvant setting[1] has raised many questions regarding the continued used of tamoxifen at all, the timing of AI use in relation to tamoxifen therapy, the optimal duration of AI use, and the patient population for which AI therapy is best suited. Treatment guidelines are useful compendiums of information that enable physicians to integrate the large body of clinical trial data in this area and facilitate choices among the different adjuvant endocrine therapies that are available. Several breast cancer treatment guidelines are currently cited by physicians and cancer centres around the world when

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Table 1 – Consensus guidelines for the adjuvant treatment of breast cancer

Guidelines	Latest version	Comments
The European Society for Medical Oncology Recommendations for Adjuvant Treatment of Breast Cancer[2]	2005	Provide strong evidence-based guidelines and a set of requirements for a basic standard of care applicable in all the countries of Europe
National Comprehensive Cancer Network (NCCN) Guidelines[3]	2006	Updated at least annually in a consensus-driven process with explicit review of the evidence by multidisciplinary panels of expert physicians from NCCN member institutions
American Society for Clinical Oncology (ASCO)[4]	2005	Experts review all the latest research on hormonal therapy for early-stage breast cancer
St. Gallen International Consensus Statement[5]	2005	Biennial guidelines are developed by multidisciplinary expert consensus of breast cancer specialists from Australia, Europe, and North America and are thought to be among the most cited guidelines available

implementing new treatment strategies for breast cancer (Table 1).[2–5] This review will compare the most popular guidelines for the adjuvant treatment of breast cancer, particularly with respect to the use of AIs. The issues of guideline adherence and how treatment recommendations may change with the emergence of new clinical data will also be discussed.

2. Adjuvant therapy

The goal of adjuvant therapy in localised breast cancer is to reduce the risk of cancer recurrence and death and to increase the chances of cure once the initial cancer has been surgically treated.[6] Systemic adjuvant treatment options for early breast cancer include chemotherapy, immunotherapy (trastuzumab), hormonal (endocrine) therapy, or combination (chemoendocrine) therapy. The choice among these potential treatment options generally depends on factors such as presence or absence of hormone receptors in the tumour (oestrogen-receptor [ER] or progesterone-receptor [PgR] status), human epidermal growth factor receptor 2 (HER-2) status, age, lymph node involvement, co-morbidities, and menopausal status; these treatment issues are addressed in guideline recommendations as described below.

3. Adjuvant chemotherapy

The National Comprehensive Cancer Network (NCCN) 2006 guidelines provide several recommendations for the use of adjuvant chemotherapy. Among them are that younger women appear to gain the most benefit from chemotherapy and that there are insufficient data to make recommendations for women over the age of 70. In the latter group of patients, the decision to implement chemotherapy should be individualised taking into account co-morbid conditions.[3] The use of chemotherapy is, thus, generally indicated for women under the age of 70. The NCCN has also made several recommendations based on retrospective analyses; the first is that doxorubicin-based chemotherapy regimens appear to be superior to non–doxorubicin-based regimens in patients with tumours overexpressing HER-2.[3] Finally, anthracycline-containing chemotherapy regimens are preferable for those patients with node-positive tumours.[3]

The 2005 St. Gallen International Consensus Panel changed the paradigm for the selection of chemotherapy as adjuvant treatment. Chemotherapy—and the type of chemotherapy—is now primarily determined by the endocrine responsiveness (tailored treatment) of the disease, whereas in the past, use of chemotherapy was mainly determined by the risk of recurrence (risk-adopted treatment). The panel concluded that most patients falling into the high-risk group are likely to receive chemotherapy unless it is contraindicated.[5] Additionally, patients in the 'endocrine-uncertain' group with intermediate risk for tumour relapse and elderly patients who are at high risk of relapse and who do not have significant co-morbidity can also be offered chemotherapy.[5] The St. Gallen panel further concluded that adequately dosed anthracycline-based chemotherapy regimens remain the acceptable standard of treatment for many women.[7] Regarding the use of taxanes, the panel suggested that no recommendations could yet be made regarding either the optimal taxane-anthracycline regimen, the best taxane, or the best taxane schedule.[7] The panel felt that a lower threshold for using taxanes was justified in cases of ER–negative or low-ER tumour status, HER-2 overexpression, or other aggressive biologic features, or concern regarding anthracycline-induced cardiotoxicity.[7] Thus, the use of taxanes was supported by the panel for patients at high risk, but most panelists did not support the use of dose-dense regimens, even in endocrine-non-responsive tumours.[5] Last, the results of four key adjuvant taxane trials, conducted in node-positive patients with 4.5 years of follow-up, suggest a 3%–7% increase in 5-year survival within the taxane treatment arms.[7] However, there remains some concern over this level-1 evidence supporting the use of taxanes with anthracyclines. Inadequate treatment comparators, ER-status imbalance, endocrine effects of chemotherapies, a possible age interaction with the taxane effect, and a reduced survival gain following Cox regression analysis, remain.[7]

3.1. *Trastuzumab*

At the time of the 2005 St. Gallen conference, results of trastuzumab trials were not available. The panelists prepared an update incorporating the results of the four key adjuvant trastuzumab trials (HERA, NSABP B-31 and NCCTG N9831, BCIRG 006, FinHER).[7–10] These trials with short follow-up all show the same signal, a reduction of recurrences by about 50% or more. Many open questions remain regarding the long-term safety, duration of treatment, concomitant or sequential use with chemotherapy and other aspects.

3.2. *Adjuvant endocrine therapy*

The overall goal of adjuvant endocrine therapy is to prevent the growth-stimulatory effects of oestrogen signalling in breast cancer cells; in postmenopausal women the two currently available therapies that accomplish this goal are tamoxifen and the third-generation AIs exemestane, anastrozole, and letrozole.[1] Adjuvant hormonal therapy with either tamoxifen or an AI is currently recommended for all women whose breast tumours contain ER, regardless of age, menopausal status, or tumour size, and independent of whether the cancer has spread to nearby lymph nodes.[11] In premenopausal patients tamoxifen remains the standard. The question whether ovarian function suppression is an essential part of the adjuvant endocrine therapy in these patients, as well as the value of chemotherapy in patients receiving combined adjuvant endocrine therapy (ovarian function suppression plus tamoxifen or an AI) are currently under investigation in a large, globally conducted group of trials (SOFT, TEXT, PERCHE trials).[12] The St. Gallen international guidelines currently state that treatment responsiveness is the primary determinant in the treatment algorithm for clinical decision-making and that postmenopausal women with endocrine-uncertain disease should receive endocrine therapy as well.[5] Even patients with ER/PgR expression of <10% of tumour cells can derive a benefit from adjuvant endocrine therapy. However, endocrine therapy is not indicated for women with hormone receptors absent in their tumours.

3.3. *Tamoxifen and the aromatase inhibitors*

Five years of tamoxifen improves disease-free survival and overall survival and was considered the gold standard of adjuvant therapy for women with early receptor-positive breast cancer for many years.[13,14] Results from two large randomised trials investigating the efficacy and safety of tamoxifen treatment for more than 5 years are expected to be reported in the near future.[15] More recently however, data from large adjuvant trials investigating the efficacy of the AIs prompted further additions to many treatment guidelines, and now the AIs are playing an increasingly important role in endocrine therapy for hormone-receptor–positive breast cancer patients.

Just 3 years ago, the 2003 American Society for Clinical Oncology (ASCO) guideline recommendations suggested that a 5-year course of tamoxifen therapy should remain as standard therapy, with AIs given only to those postmenopausal women with a relative or absolute contraindication to tamoxifen.[16] However, with the emergence of new data, the 2005 ASCO guidelines, the current St. Gallen international guidelines, the NCCN guidelines, and the European Society for Medical Oncology (ESMO) recommendations now recommend an AI as suitable in the course of treatment of postmenopausal women with endocrine-responsive early-stage breast cancer.[2–5] The current NCCN guidelines recommend the use of an AI (letrozole or anastrozole) as an initial adjuvant therapy, as sequential therapy with tamoxifen (anastrozole or exemestane), or as an extended therapy (letrozole).[3]

One important issue for breast cancer patients who completed the initial 5 years of adjuvant tamoxifen therapy was that they had no other options to further reduce their risk of breast cancer relapse. Importantly, the 2005 ASCO guidelines now recommend at least 2.5 years of extended adjuvant letrozole for such patients.[4] Presently, letrozole is the only AI that has been recommended and approved for this extended adjuvant indication in any of the three major guidelines (ASCO, NCCN, St. Gallen) based on the results of the MA.17 study.[17] The optimal duration of letrozole as extended adjuvant therapy is unknown, but recent data from a cohort analysis support the use of extended adjuvant letrozole at least out to 4 years.[18]

Neither the optimal timing nor the duration of AI therapy has been established, but nonetheless the 2005 ASCO guidelines recommend that optimal adjuvant hormonal therapy should include an AI either as initial therapy or after treatment with tamoxifen.[4] According to the current guidelines, the use of tamoxifen alone for 5 years should be limited to those who decline or who have a contraindication for AIs, although taking an AI for more than 5 years is not yet warranted due to lack of data.[4,8] The Breast International Group (BIG) 1–98 trial is another important study that should resolve the issue of when and how AIs should be used in relation to tamoxifen. Briefly, 5 years of letrozole or tamoxifen monotherapy will be compared with each other, as well as with two sequential treatment regimens (letrozole 2 years then tamoxifen 3 years or tamoxifen 2 years then letrozole 3 years).[19] Results of the primary core analysis of BIG 1–98 were unavailable and, therefore, not included in the 2005 ASCO guidelines. The 2005 St. Gallen international guidelines and the updated NCCN guidelines, however, have acknowledged the first results from the monotherapy groups in the BIG 1–98 trial, including the improvement in disease-free survival and the significant improvement in distant disease-free survival observed for letrozole compared with tamoxifen.[3,5,19]

In summary, the major consensus guidelines now recognise the superiority of the AIs over tamoxifen in the adjuvant setting, and the AIs can now be integrated into the array of treatment options. Notably, a significant change in the algorithm of selection for adjuvant therapy has been made by the St. Gallen International Consensus Panel in the 2005 guidelines. In lieu of the earlier guideline emphasising risk assessment for early breast cancer, the current consideration affirmed by the panel was based on three possible categories of endocrine responsiveness: endocrine responsive, endocrine unresponsive, and tumours of uncertain responsiveness. This change has important implications for the increased use of AI therapy, particularly in those patients whose tumours are deemed endocrine-responsive.[5]

The NCCN guidelines emphasise that for adjuvant hormonal therapy in postmenopausal patients, anastrozole or letrozole for 5 years may be used, or tamoxifen for 4.5–5 years followed by letrozole for 5 years. Another option in this postmenopausal setting is tamoxifen for 2–3 years followed by exemestane to complete 5 years of adjuvant hormonal therapy.[3] Similarly, the 2005 St. Gallen guidelines recommend the following options for high-risk or intermediate-risk postmenopausal patients with hormone-responsive or doubtful disease requiring endocrine therapy:

- Up to 5 years of AI monotherapy (anastrozole or letrozole)
- Tamoxifen for 2–3 years and switch to an AI (exemestane, anastrozole) to complete 5 years of therapy
- Five years of tamoxifen therapy followed by extended treatment with an AI (letrozole)

With regard to low-risk patients (eg, node-negative, tumour ⩽0.5 or 1 cm, well-differentiated, no unfavourable features), the NCCN 2006 and the St. Gallen international guidelines recommend either no adjuvant therapy, an AI, or tamoxifen to reduce the risk of recurrence.[3,5] Thus, AIs are suitable options even for patients at low risk of recurrence. Regarding adjuvant hormonal therapy in the premenopausal setting, tamoxifen for 5 years is indicated with or without ovarian suppression or ablation. The NCCN guideline also emphasises that AIs are not currently the standard in women with functioning ovaries and that AIs should only be used in premenopausal women in the context of clinical trials.[3] The St. Gallen panellists also do not recommend AIs in premenopausal patients even in conjunction with ovarian function suppression as standard therapy due to the lack of data.[5] However they concluded that AIs and ovarian function suppression are a suitable option for patients with contraindications for tamoxifen.[5]

3.4. *Chemotherapy and endocrine therapy (chemoendocrine therapy)*

There may be a benefit in some patients from combining chemotherapy and endocrine therapy regimens. According to the 2005 ESMO recommendations, endocrine-responsive and endocrine-nonresponsive premenopausal and postmenopausal patients are candidates for adjuvant chemotherapy in a combination regimen.[2] According to NCCN guidelines, chemotherapy and hormonal therapy have additive benefits, and the absolute benefit from chemotherapy may be small. It should be noted that there is a clear difference between NCCN and the St. Gallen international guidelines. The NCCN and other guidelines do not address the issue of chemoendocrine treatment in endocrine-responsive and endocrine-nonresponsive disease separately. The tailored approach according to endocrine responsiveness is a unique feature of the St. Gallen 2005 guidelines. However, individualised decisions on whether to add chemotherapy to hormonal therapy are recommended, based upon a patient's prognosis and the expected incremental benefit of chemotherapy.[3]

Various guidelines agree that adjuvant therapy should be given sequentially, that is, hormonal therapy (e.g. tamoxifen) should begin after chemotherapy has been completed.[2,3] The 2005 St. Gallen international conference recommended chemotherapy followed by endocrine therapy for high-risk and intermediate-risk patients with endocrine-responsive or endocrine-uncertain disease.[5]

4. Unresolved issues and data on the horizon

The results of ongoing studies will be needed to establish the optimal AI treatment strategy and will certainly stimulate further refinement of treatment guidelines. Currently, it is unclear whether initial treatment with an AI is superior, equivalent, or inferior in relation to switching from tamoxifen to an AI after some fixed time point.[4] Forthcoming data from the sequential arms of the BIG 1-98 trial will provide a definitive answer to this question. The Tamoxifen Exemestane Adjuvant Multicenter (TEAM) trial (tamoxifen followed by exemestane versus exemestane for a total of 5 years) will also generate data to answer the question of whether to use AIs upfront or in a switching regimen.

The results from future and ongoing trials will help to determine the optimal duration of AI therapy following surgery or following treatment with tamoxifen for women with hormone-receptor–positive breast cancer. A re-randomisation of patients in the MA.17 trial is under way and will determine whether longer treatment with letrozole after 5 years of tamoxifen conveys a continued benefit. Based on the 30-month follow-up results from MA.17, the ASCO guidelines support the use of letrozole for at least 2.5 years in patients who have completed tamoxifen therapy, without specifically recommending any duration of letrozole treatment. Results from a study investigating impact of duration of letrozole therapy on outcomes in MA.17 show that the longer patients are exposed to letrozole, the greater the benefit (up to 4 years), whereas those on placebo after 5 years of tamoxifen show a steadily increased risk of disease recurrence over time.[18] These results seem to support the use of extended adjuvant letrozole therapy beyond 2.5 years.

Another important unresolved issue concerns the identification of those patients who are most likely to benefit from AI therapy. Further results from ongoing AI trials might help identify patient populations that may benefit from a particular adjuvant therapy (i.e. node-positive, ER/PgR status, HER-2 status). Subgroups of patients on tamoxifen can be identified who appear to be at a higher risk of early relapse and who might consequently benefit from upfront AI therapy. Results of a study recently presented at the San Antonio Breast Cancer Symposium (SABCS) showed that patients with low ER positivity, grade 3 pathology, and those patients with lymph node involvement are at increased risk for earlier relapse (Table 2).[20] Of note, prospectively planned analyses have shown letrozole to have a particular benefit for patients at early risk

Table 2 – Relapse rates according to risk group among 4159 women on tamoxifen following adequate locoregional therapy with or without chemotherapy[20] (Reprinted with permission)

	N	2.5 Year relapse rate	P Value
Grade			
I	544	1.1	<0.001
II	2135	5.3	
III	1242	13.4	
Oestrogen-receptor status			0.005
Mod/high	2990	6.5	
Low	393	14.5	
Number of + nodes			<0.001
0	1962	3.7	
1–3	1650	8.5	
4+	543	17.2	

of relapse such as those who had received chemotherapy or those with node-positive disease.[17,19]

Conversely, for patients at lower risk of early recurrence, a sequential regimen of tamoxifen upfront, followed by an AI, can be envisioned.[17] It has been suggested that patients with ER-positive/PgR-negative, and/or HER-2–positive tumours appear to have an increased benefit with AI therapy compared with tamoxifen therapy.[2,4] Retrospective, exploratory data from the Adjuvant Tamoxifen Alone or in Combination (ATAC) trial suggest that a benefit of anastrozole over tamoxifen is confined to the ER-positive/PgR-negative subgroup (for time to recurrence, hazard ratio (HR) = 0.84 versus 0.45, respectively).[21] In contrast, data from local, as well as from a central assessment of ER/PgR in the BIG 1-98 trial show a benefit of letrozole irrespective of PgR status.[19,22] The BIG 1-98 central assessment of ER/PgR and HER-2 status is the first ever undertaken for an adjuvant AI trial. At present, this analysis of nearly 4400 tumours has shown that the small group of patients with HER-2 overexpression/amplification in the tumour had a higher rate of recurrence with both treatments. PgR status in ER-positive tumours did not predict responsiveness to letrozole when compared with tamoxifen. Thus, at present, neither HER-2 status nor PgR status help to select letrozole over tamoxifen for postmenopausal patients with ER-positive tumours.[22]

Gene expression profiling is now under investigation as a potential means to identify patients who are at high risk of relapse, or who may be more likely to fail endocrine therapies. The promise of gene profiling technology is that it may one day be possible to identify those patients for whom endocrine therapy is likely to have the greatest benefit; it has even been proposed that such technology may be an alternative to clinical guidelines. Nonetheless, the technology, still in the early stages of development, will require more refinement and prospective validation.[23]

Tamoxifen and AIs have different side-effect profiles. In contrast with tamoxifen, the long-term side effects of the AIs are under investigation.[4] The re-randomisation of patients in the MA.17 trial will provide important information about letrozole's long-term safety in comparison with placebo. The Zometa-Femara Adjuvant Synergy trial (Z-FAST) is investigating the effect of delayed or upfront treatment with zoledronic acid, a potent bisphosphonate, on bone mineral density in patients undergoing adjuvant letrozole treatment.[24] Early results indicate that upfront zoledronic acid treatment can effectively manage and/or prevent AI-associated bone loss.[24] Smaller safety substudies in selected patient populations investigating bone health, cognitive function, and lipid metabolism are ongoing. Longer follow-up and careful analysis of side effects, in particular deaths without recurrence, in all AI trials will also contribute to the long-term safety data.

Several other trials in the accrual phase will further establish the safety of adjuvant AI therapy. The MAP.3 Prevention trial is currently comparing exemestane with placebo for 5 years in women at high risk of developing breast cancer.[25–27] The International Breast Intervention Study II (IBIS II) is another large study, currently still open to recruitment, evaluating the effect of anastrozole versus placebo in 6000 postmenopausal women at increased risk of breast cancer.[25,27] Finally the MA.27 trial, comparing anastrozole with exemestane and the Femara versus Anastrozole Clinical Evaluation (FACE) trial comparing anastrozole with letrozole in node-positive patients will help to determine if there are differences in efficacy and safety between the AIs.[28]

4.1. *Adherence to guidelines*

Despite the widespread availability of treatment guidelines, it is evident that there is room for improvement in overall attitudes toward clinical guideline development. One study of Canadian oncologists found that 73% of respondents thought of guidelines as 'very helpful' as an educational tool and about 50% of the respondents found them very helpful as a guide to clinical practice and as a tool for resource mobilisation.[29] Despite this, results from the same study suggested that less than a quarter of the responding physicians formulated their opinions of clinical trial data after waiting for clinical guidelines to become available, whereas most reached their overall conclusions through consultation with colleagues or through their own independent assessment (Fig. 1).[29]

The need for more effective practical implementation of treatment guidelines is crucial. An Italian study found that, despite guideline recommendations, the frequency of administration of adjuvant therapy for early breast cancer by physicians was low, indicating that adherence to guidelines is suboptimal.[30] Under-treatment was most commonly observed in node-negative patients, at intermediate/high risk,

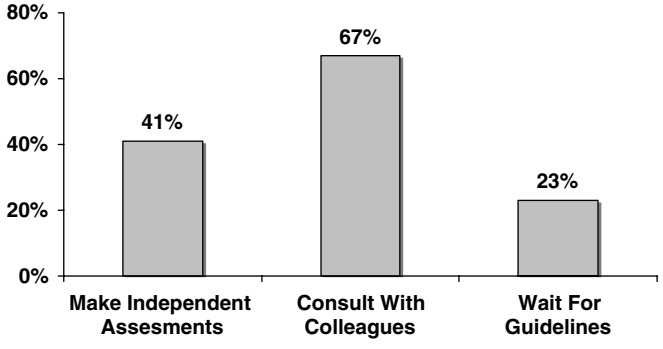

Fig. 1 – Oncologists' opinions (*N* = 739; response rate 21%) of treatment guidelines with respect to formulating opinions regarding clinical trial results.[29]

Table 3 – Breast cancer specific survival among women according to risk category and by treatment within consensus guidelines and otherwise (comparisons with consensus-treated minimal risk)[33]

Treatment	Intermediate risk Hazard ratio (*P* Value)	High risk Hazard ratio (*P* Value)
Within consensus guidelines	1.9 ($P = 0.2$)	5.5 ($P < 0.0005$)
Otherwise	2.4 ($P = 0.2$)	7.4 ($P < 0.0005$)

where no treatment was prescribed in between 21% and 45% of cases.[30] Similarly, a study evaluating the use of adjuvant systemic therapies in women surgically treated for breast cancer revealed that approximately one out of every five patients did not receive endocrine therapy as suggested by the most current St. Gallen international guidelines available at the time.[31,32] Moreover, 12% of patients with hormone-receptor–negative disease were inappropriately prescribed endocrine therapy.[31]

The impact of such nonadherence to treatment recommendations should not be underestimated. The findings of a Canadian study of 1541 women with a 6.8-year follow-up period have indeed shown that compliance with guidelines was an independent and significant predictor of survival (Table 3).[33]

Another study compared actual care received by breast cancer patients ($N = 4395$) with evidence from the NCCN clinical guidelines and meta-analysis results.[34] Optimal or NCCN-based treatment was provided to fewer than half (45%) of the patients, whereas the majority of patients in each disease stage (with the exception of those with ductal carcinoma *in situ*) were not treated according to guidelines or in accordance with data from meta-analysis.[34] The low level of adherence to and implementation of guidelines observed in these studies may be a result of ineffective continuing medical education, inadequate organisation and delivery systems, and/or insufficient health-system support for clinicians.[1,34]

5. Conclusions

Treatment guidelines are useful tools to inform the medical community of the rapidly evolving progress being made in breast cancer therapeutics, and to effectively summarise emergent results from ongoing clinical trials that would otherwise await publication of final study results. It is clear that lack of adherence to such guidelines may result in an inappropriate use of some therapies and/or omission of some patients from presently most effective therapy, resulting in a significant public-health impact.[31] Moreover, recent data suggest that promoting adherence to guidelines for treatment is an effective strategy for disease control that can significantly improve survival.[33] Guidelines also provide a basis for the physician to decide among treatment strategies and to present a range of therapeutic options to the patient. Ultimately, patient lifestyle preferences may influence the choice of treatment, and all available options for adjuvant therapy should be discussed in order to determine which therapy will provide the greatest benefit to the patient. Given the potential impact of treatment guidelines, further study is needed to determine those factors governing variability in adherence to guidelines and the implementation of national and local guideline recommendations.

Treatment guidelines are also important because they provide the clinician with a series of recommendations developed from the consensus opinions of international experts based on their interpretation of the most recent clinical trial data. Since 1978 the St. Gallen International Conferences have focused on developing consensus opinions for the management of early breast cancer, and these are now recognised as the most respected treatment guidelines for this disease internationally. In the United States, they are strongly supported by both the NCCN guidelines and the ASCO Technology Assessment of 2004. Despite some differences in the focus of these guidelines, all are providing updated references and recommendations to guide optimal use of systemic adjuvant therapies. One of the fundamental changes in the St. Gallen International Consensus on Primary Treatment of Early Breast Cancer 2005 was to identify endocrine responsiveness as the first step in determining the most appropriate course of treatment. This is in contrast with other guidelines. The other guidelines commence with risk assessment, which is now considered less important in influencing treatment choice. In consequence, chemotherapy is the main modality in hormone-nonresponsive breast cancer. There is a large concordance regarding incorporation of AIs as part of endocrine treatment of postmenopausal patients among the guidelines. The change in the prescription pattern of endocrine agents will obviously depend on further information emerging from ongoing and new trials and will also depend on resources and priorities of the national health care systems.

Conflict of interest statement

None declared.

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