Review Article

A review of endocrine therapy in early estrogen receptor-positive breast cancer by St. Gallen Breast Cancer Conference 2021

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Abstract: Estrogen receptor (ER) positive (+) breast cancer is heterogeneous; thus, corresponding therapeutic regimens must differ according to the individual characteristics of ER+ breast cancer patients. At the 17th international St. Gallen Breast Cancer Conference (SG-BCC) in 2021, experts voted on numerous critical issues in relation to the use of neoadjuvant endocrine therapy (NET) and adjuvant endocrine therapy (AET) in the treatment of ER+ breast cancer. We interpreted the critical issues related to NET and AET according to the voting results of the 2021 SG-BCC and clinical practice in China. Specifically, we considered the following 8 points: (I) the selection of prognostic indicators for NET; (II) the selection of a NET population based on Ki-67; (III) the selection of polygenic testing combined with Ki-67 in the exemption of neoadjuvant chemotherapy; (IV) the selection of an AET population based on ER expression level and tumor size; (V) the selection of ovarian function suppression for a premenopausal population; (VI) the selection of early stage intensive AET for a postmenopausal population; (VII) the selection of an extended AET population; and (VIII) the selection of individuals exempt from chemotherapy. We combined the results of existing clinical studies to analyze the reasons why the experts at the 2021 SG-BCC voted on the above issues, and how clinicians should use the voting results of the 2021 SG-BCC poll to select therapeutic regimens for patients. Decisions to use ET to treat ER+ breast cancer patients should always balance individualized therapy and standardized therapy.

Keywords: Adjuvant endocrine therapy (AET); estrogen receptor (ER); positive breast cancer; neoadjuvant endocrine therapy (NET); SG-BCC 2021

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Introduction

Estrogen receptor (ER) positive (+), human epidermal growth factor receptor 2 negative (HER2–) breast cancer is the most common type of breast cancer (1), and accounts for 65% of breast cancer in women aged under 50, and 75% of breast cancer in women aged 50 and over. ER+ breast cancer is heterogeneous; differences in ER expression level, progesterone receptor (PR) expression, histological grade, the degree of proliferation (Ki-67), and the type and frequency of genomic changes in different patients lead to different degrees of disease progression and prognoses. Thus, the corresponding therapeutic regimens for ER+ breast cancer should differ according to the individual characteristics of patients. At the 17th international St.

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Gallen Breast Cancer Conference (SG-BCC) in 2021, experts voted on numerous critical issues in relation to the use of neoadjuvant endocrine therapy (NET) and adjuvant endocrine therapy (AET) in the treatment of ER+ breast cancer. All clinicians and researchers should give consideration to the outcome of this poll.

In this article, we interpret the critical issues related to NET and AET according to the voting results of the 2021 SG-BCC and clinical practice in China. Specifically, we consider the following 8 points: (I) the selection of prognostic indicators for NET; (II) the selection of a NET population based on Ki-67; (III) the selection of polygenic testing combined with Ki-67 in the exemption of neoadjuvant chemotherapy; (IV) the selection of an AET population based on ER expression level and tumor size; (V) the selection of ovarian function suppression (OFS) for a premenopausal population; (VI) the selection of early stage intensive AET for a postmenopausal population; (VII) the selection of an extended AET population; and (VIII) the selection of individuals exempt from chemotherapy. The relevant questions and corresponding voting results for each point are set out in *Table 1*.

NET for ER+ breast cancer patients

The selection of prognostic indicators for NET

Pathologic complete response (pCR) has been used for more than a decade as an alternative endpoint for clinical trials and drug approval in early breast cancer; however, a majority of experts (83.05%) surveyed in the 2021 SG-BCC poll were of the view that the endpoints of the standard regimen should be longer-term event-free survival (EFS) and overall survival (OS) rather than pCR. In relation to luminal A breast cancer, a clinical study (2) showed that there was little difference between the prognoses of pCR and non-PCR patients, and thus pCR should not be used as a prognostic indicator. The development of new predictors associated with clinical outcomes is urgent and will provide opportunities to develop new strategies to reverse resistance to NET and identify response/resistance biomarkers in translational research.

The role of Ki-67 as a marker for evaluating the efficacy of NET

Ki-67 is a marker commonly used clinically to evaluate tumor proliferation status in breast cancer patients, and is easy to stain and score. However, currently, there is no consensus as to the threshold of Ki-67 in NET for breast cancer. ACOSCG Z1031, POETIC, and ADAPT state that the threshold of Ki-67 is 10%, while P024, PALLET and NeoMonarch state that the threshold of Ki-67 is 2.7%. Nearly 70% of experts surveyed in the 2021 SG-BCC poll agreed that Ki-67 should be used as a routine measure during or after the administration of NET to evaluate its efficacy, and that the dynamic change of Ki-67 after 2 weeks of treatment could be used to evaluate prognosis. Notably, the POETIC study (3) showed that the 5-year recurrence risk was 19.6% in those with a high baseline Ki-67 and a high Ki-67 after 2 weeks of ET, but only 8.9% in those with a high baseline Ki-67 and a low Ki-67 after 2 weeks of ET. The identification of high-risk populations is critical to subsequent treatment choices. In addition to Ki-67, the predictive effects of the Preoperative Endocrine Prognosis Index (PEPI) on the efficacy and recurrence risk of NET for ER+ breast cancer was verified by the FELINE and ALTERNATE studies.

The value of polygenic testing combined with Ki-67 in the exemption of neoadjuvant chemotherapy in ER+ breast cancer

The applications of Ki-67 monitoring in NET are not limited to those mentioned above. The ADAPT study (4) combined Ki-67 with genetic testing and showed that the 5-year invasive disease-free survival (iDFS) rate of patients at medium risk [with a recurrence score (RS) of 12–25] and a Ki-67 <10% within 3–4 weeks, who received ET without chemotherapy, reached 92.6%. Notably, this rate did not differ significantly from that of patients with a RS of 0–11, who had a 5-year iDFS of 93.9%. These results further highlight the significance of detecting dynamic changes of Ki-67 after NET. The ADAPT study also showed the ability of polygenic testing tools to assist in the screening of patients for neoadjuvant studies. Thus, more than 70% of experts surveyed at the 2021 SG-BCC were of the view that the genomic analysis of needle biopsies can be used to select patients with ER+ breast cancer for NET and chemotherapy, and more than 90% of experts were of the view that chemotherapy is no better than ET in the treatment of breast cancer patients with a low genomic risk.

AET for ER+ breast cancer patients

Threshold selection for AET population

In selecting patients to undergo AET, the threshold of ER+

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Table 1 Summarization about the crucial voting results of neoadjuvant and adjuvant endocrine therapy in SG-BCC 2021

Question	Majority vote
NET for ER+ breast cancer patients	
The selection of prognostic indicators for NET	
The standard regimen should be based on longer-term EFS and OS endpoints rather than pCR or not	Yes
The selection of NET based on Ki-67	
Ki-67 should be used as a routine measure during or after administration to evaluate the efficacy of NET or not	Yes
The dynamic change of Ki-67 after two weeks of treatment could be used to evaluate the prognosis or not	Yes
The selection of polygenic testing combined with Ki-67 in the exemption of neoadjuvant chemotherapy	
Genomic analysis of needle biopsies can be used to select patients with ER+ breast cancer for neoadjuvant endocrine therapy and chemotherapy or not	Yes
Chemotherapy is better than ET for breast cancer patients with low genomic risk or not	No
AET for ER+ breast cancer patients	
The selection of AET population based on ER expression level and the size of tumor	
Patients with ER-positive expression ≥1% or ≥10% are suitable for AET	50% supported 1% and 50% supported 10%
Negative lymph nodes infiltration patients with tumor micro infiltration can choose AET or not	Yes
The selection of OFS for premenopausal population	
Women with premenopausal at clinical stage II ER+ breast cancer should receive OFS or not	Yes
All premenopausal patients or only patients at high risk (<40 years, lymph nodes positively infiltrating, high Ki-67 and/or Luminal B or median/high-risk genomic characteristics) with ER+ breast cancer at clinical stage II should receive OFS	42.59% supported all patients and 51.85% supported patients at high risk
The possible contribution of chemotherapy-induced OFS to the effectiveness of chemotherapy	41.86% of the experts agreed that the contribution was at least more than 75%
The recommended treatment regimen for premenopausal patients with negative lymph nodes infiltration and RS 16–25 or low genetic risk	53.6% supported OFS combined with tamoxifen or AIs
The recommended treatment regimen for premenopausal patients with 1–3 positive lymph nodes infiltration and RS ≤25 or low genetic risk	30.19% supported chemotherapy combined with ET, 16.98% supported OFS combined with ET
The selection of early-stage intensive AET for postmenopausal population	
Adjuvant treatment of abemaciclib in ER+ patients with 4 or more positive lymph nodes infiltration or not	Yes
Adjuvant treatment of abemaciclib for patients who only met the standard criteria for monarchE cohort2 or not	No
Ki-67 should be used to guide CDK4/6 inhibitors use or not	No

Table 1 (*continued*)

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Table 1 (*continued*)

Question	Majority vote
The selection of extended AET population	
The optimal course of ET	Longer than 5 years
The recommended treatment regimen for premenopausal high-risk patients who had received 5 years of OFS combined with tamoxifen treatment	44.9% supported tamoxifen alone, 40.82% supported OFS combined with AI or AI alone
The selection of people exempted from chemotherapy in AET	
Chemotherapy should be required for postmenopausal patients whose clinical manifestations meet MINDACT, TAILORx, RxPONDER and similar trials at low risk and/or with RS <25 or not	No
Chemotherapy should be required for patients with 3 or more positive lymph nodes infiltration or pT3pN1 or not	48.94% supported yes

NET, neoadjuvant endocrine therapy; AET, adjuvant endocrine therapy; EFS, event-free survival; OS, overall survival; pCR, pathologic complete response; ER, estrogen receptor; ET, endocrine therapy; OFS, ovarian function suppression; RS, recurrence score.

expression is the key screening marker. 50% of experts surveyed in the2021 SG-BCC poll were of the view that patients with an ER+ expression ≥1% were suitable for AET, while the other 50% of experts were of the view that patients with an ER+ expression ≥10% were suitable for AET. The question of how to determine the ER+ expression threshold has been the focus of extensive AET research. In 2011, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines (5) suggested that the threshold of ER+ expression should be 1%. A study (6) showed that patients who received chemotherapy with low ER expression (ER expression <10%) of HER2- breast cancer had a poor clinical prognosis, and that the time to recurrence (TTR) and OS rate of the group with an ER expression ≥10% were higher than those of the 1% ≤ ER <10% and ER <1% expression group (it should be noted there was no difference between these 2 groups). In terms of AET, a meta-analysis (7) showed no difference between the OS of patients with a low ER expression (1–9%) after 5 years of AET and the OS of patients who did not undergo ET (P=0.684). In the diagnosis and treatment process, Chinese doctors are of the view that patients with a 10% positive ER expression rate would benefit from ET, and 1% as the expansion of ET population makes patients not to miss the opportunity of ET.

In terms of the threshold selection of tumor size, more than 50% of experts surveyed in the 2021 SG-BCC poll were of the view that ER+ negative lymph node infiltration patients with tumor micro infiltration could choose AET either luminal A or luminal B. In contrast to the controversial issue of the selection of an ER+ threshold, most experts were of the view that an enlarged population is acceptable at the tumor size level of AET.

The proper application of intensive AET

OFS in the premenopausal population

In our clinical work, we have observed that Chinese breast cancer patients who attend our clinic are young in age. In relation to these premenopausal ER+ breast cancer patients, the choice of OFS is a topic of concern for many researchers. In the 2021 SG-BCC poll, more than 70% of experts agreed that premenopausal women at clinical stage II ER+ breast cancer should receive OFS, and more than 90% agreed that patients younger than 40 years old should receive OFS. However, experts' opinions differed as to whether the entire premenopausal population or high-risk patients should receive OFS.

The SOFT (8) study provides insights into this issue. The SOFT study explored the efficacy of OFS and the efficacy of OFS combined with exemestane in premenopausal patients, and found no improvement in the 5-year disease-free survival (DFS) rates between the OFS combined with tamoxifen group and the tamoxifen monotherapy group; however, the benefits of breast cancer-free interphase and distant recurrence-free interphase (DRFI) were observed in the chemotherapy patients. Thus, OFS and chemotherapy appear to benefit patients at a high risk of recurrence. Following the results of the 8-year SOFT study (9), investigators observed a population-wide benefit in DFS when OFS was combined with tamoxifen, and an OS benefit in chemotherapy patients; however, no significant

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DRFI benefit was observed in patients who did not receive chemotherapy. In the 2021 SG-BCC poll, experts considered the possible contribution of chemotherapy-induced OFS to the effectiveness of chemotherapy overall, and more than 40% agreed that the contribution was more than 75%. The ASTRRA (10) study also confirmed the benefits of OFS for chemotherapy patients.

In the 2021 SG-BCC poll, experts' opinions differed in relation to premenopausal patients with 1–3 positive lymph nodes and a RS of <25 or a low genetic risk. The combined analysis of the SOFT and TEXT studies (11) provides guidance on the selection of treatment combinations for premenopausal patients (OFS combined with exemestane or tamoxifen). Therefore, the questions of whether all premenopausal patients should receive OFS combined with aromatase inhibitors (AIs) and whether low-risk patients who do not undergo chemotherapy should choose OFS need to be considered when choosing therapeutic regimens for young patients with ER+ breast cancer.

CDK4/6 inhibitors in the postmenopausal population

AI is currently the gold standard of adjuvant therapy for postmenopausal ER+ early-stage breast cancer. Promising clinical trial results of CDK4/6 inhibitors in recent years have led to its rapid development in clinical use. Ongoing clinical studies include PENELOPE-B, PALLAS, monarchE and NATALEE (12). Among these, the monarchE study compared the efficacy of abemaciclib combined with standard ET, and a standard ET regimen, and found a 2-year iDFS of 92.3% (with a 3% absolute benefit) in the abemaciclib group. In the 2021 SG-BCC poll, more than 50% of experts supported the adjuvant treatment of abemaciclib in ER+ patients with 4 or more positive lymph nodes.

However, for patients who only met the standard criteria for monarchE cohort2, more than half of the experts did not support adjuvant therapy with abemaciclib. This relatively conservative opinion was similar to experts' opinions on the use of the Ki-67 (in combination with other prognostic markers) to guide adjuvant therapy with CDK4/6 inhibitors. Notably, more than 60% of experts agreed that Ki-67 should not be used to guide CDK4/6 inhibitor use. In the monarchE subgroup, the high Ki-67 subgroup had a worse prognosis, and the abemaciclib-treated group had a higher 2-year iDFS than the ET alone group (91.3% *vs.* 86.1%).

There are several reasons why despite the encouraging results of the monarchE study experts failed to vote in favor of expanding the population for the early use of CDK4/6 inhibitors. First, in the studies of AET and CDK4/6 inhibitors mentioned above, a high risk was not the only factor affecting prognosis and remission. Second, the intensity of ET is not sufficient (monarchE used OFS in 21.7% of cases, tamoxifen in 30% of cases, and AI in 70% of cases). Third, the effect of current studies on advanced recurrence is not clear. The time to start CDK4/6 inhibitors after the recurrence of ER+ breast cancer 5 years later (about 50%) and the duration of the treatment are uncertain. Fourth, different CDK4/6 inhibitors may have different therapeutic effects on the intension of early AET due to different mechanisms. Researchers should continue to focus on the longer survival results of patients in these clinical studies to ensure the proper use of CDK4/6 inhibitors in the postmenopausal population.

Extending the duration of AET

In the 2021 SG-BCC poll, most experts supported a long course of ET that was not limited to 5 years. In relation to premenopausal high-risk patients who had received 5 years of OFS combined with tamoxifen treatment, most experts chose tamoxifen alone; however, some experts chose OFS combined with AI or AI alone. In relation to breast cancer patients with ER+ HER2- and positive lymph node infiltration, more than 80% of experts were of the view that the optimal course of ET was longer than 5 years. In relation to the use of prolonged ET, many clinical studies (13) have provided reference data; for example, ATLAS and ATTOM examined the efficacy of sequential tamoxifen after 5 years of tamoxifen treatment, NSABP B-33 studied sequential AI after 5 years of tamoxifen treatment, and NSABP B-42 studied sequential AI after 5 years of AI/tamoxifen treatment. These studies all found that, to varying degrees, the intensification of AET can lead to a breakthrough in extending the duration of treatment.

The selection of chemotherapy exempted from AET

In the 2021 SG-BCC poll, the issue of whether patients with a low risk of recurrence should be exempted from chemotherapy was also a key point. Overall patients in 3 related studies (MINDACT, TAILORx and RxPONDER) (14) were found not to benefit from chemotherapy, and nearly 80% of experts did not support chemotherapy in postmenopausal patients whose clinical manifestations met those of MINDACT, TAILORx, RxPONDER and similar trials at low risk and/or with a RS <25. However, experts' opinions changed when the patient population was

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segmented. In relation to patients with 3 or more positive lymph nodes or pT3pN1, more than 40% of the experts were of the view that this patient population required chemotherapy. Thus, even in low-risk patients with a RS of <25, the decision as to whether chemotherapy is not necessary in the treatment regimen must be decided on a case-by-case basis.

Conclusions

In this review, we summarized and discussed the crucial issues considered at the 2021 SG-BCC, including how to administer chemotherapy to patients with different recurrence risks and how to properly use CDK4/6 inhibitors in postmenopausal patients and OFS in premenopausal patients undergoing adjuvant therapy for ER+ breast cancer. In relation neoadjuvant therapy, clinicians need to pay attention to the questions of how to predict the prognosis of patients according to the dynamic changes of Ki-67 and the duration of intensive ET. A series of clinical studies in the field of NET and AET have provided evidence for the selection of therapeutic screening criteria and effective prognostic markers by subdividing the efficacy evaluation results into population groups. Overall, in the process of ET for ER+ breast cancer, we should always balance individualized therapy and standardized therapy, and pay attention to progress in relevant clinical research.

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