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Systemic Treatment of Patients with Metastatic Breast Cancer

ASCO Resource-Stratified Guideline

Al Sukhun S et al.

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Background & Methodology

Introduction

- The purpose of this guideline is to provide expert guidance on the systemic treatment of metastatic breast cancer to clinicians, public health leaders, patients, and policymakers in resource-constrained settings.
- This guideline's target population is adult patients with metastatic breast cancer in resource-constrained settings and focuses on medical treatment.
- Different regions of the world, both among and within countries, have variable access to diagnosis and treatment of breast cancer. In addition, patients' access to medicines may change quickly.
- As a result of these disparities, the ASCO Resource-Stratified Guideline Advisory Group chose metastatic breast cancer as a priority topic for guideline development.

Introduction

- ASCO has established a process for development of resource-stratified guidelines,¹ which includes mixed methods of evidence-based guideline development, adaptation of the clinical practice guidelines of other organizations, and formal expert consensus.
- This guideline summarizes the results of that process and presents resource-stratified recommendations

Framework of Resource Stratification

Setting	Description
Basic	Core resources or fundamental services that are absolutely necessary for any public health/primary health care system to function; basic-level services typically are applied in a single clinical interaction. Vaccination is feasible for highest need populations.
Limited	Second-tier resources or services that are intended to produce major improvements in outcome such as incidence and cost-effectiveness and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple interactions. Universal public health interventions feasible for greater percentage of population than primary target group.
Enhanced	Third-tier resources or services that are optional but important; enhanced-level resources should produce further improvements in outcome and increase the number and quality of options and individual choice. (Perhaps ability to track patients and links to registries).
Maximal	May use high-resource settings' guidelines. High-level/state-of-the art resources or services that may be used/available in some high-resource countries and/or may be recommended by high-resource setting guidelines that do not adapt to resource constraints but that nonetheless should be considered a lower priority than those resources or services listed in the other categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment.

NOTE. Data adapted.^{2,3} To be useful, maximal-level resources typically depend on the existence and functionality of all lower level resources. Maximal level recommendations are not included in this guideline

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) resource-stratified guideline process includes:
 - adaptation of systematic literature review-based clinical practice guidelines
 - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
 - final guideline approval by ASCO EBMC
- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology
- More information on the ASCO Resource-Stratified Guidelines methodology can be found in the 2018 JCO Global Oncology article by Al-Sukhun et al¹:
<https://ascopubs.org/doi/full/10.1200/JGO.18.00113>

Adapted Guidelines

- The recommendations were developed through a review of existing Maximal setting ASCO-published guidelines⁴⁻¹⁰ and clinical experience of the panel of experts.
- A total of four ASCO guidelines on medical treatment of patients with metastatic breast cancer were found.
- The Expert Panel was aware of three rapid updates published in 2022,^{7,8,11} however, since this RSG development started before those publications, the recommendations in this guideline do not necessarily reflect those updates (which are relevant only to Maximal settings).
- These ASCO Maximal setting guidelines cover treatment of patients with metastatic breast cancer, both female and male, and with the following sub-types:
 1. HR-positive
 2. HER-negative and either endocrine-pretreated or HR-negative (the latter referred to triple-negative in this guideline)
 3. HER2-positive

Guideline Question, Target Population & Audience

Overarching Guideline Question

- What is the optimal treatment for patients diagnosed with metastatic breast cancer in resource-constrained settings?

Target Population

- Adult patients with metastatic breast cancer in resource-constrained settings

Target Audience

- Clinicians, public health leaders, patients, and policymakers in resource-constrained settings

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Summary of Recommendations

Summary of Recommendations

General Notes.

1. Palliative care needs should be addressed for all patients at presentation of MBC, including situations in which no antineoplastic interventions are accessible.
2. Patients who are premenopausal can only receive aromatase inhibitors if accompanied by ovarian ablation or ovarian suppression.
3. Clinicians should recommend treatment according to pathological and biomarker features when quality (following established guidelines) testing results are available.
4. Cases should be discussed using a multidisciplinary approach with the core team including the surgeon, pathologist, oncologist, and radiation oncologist.

Summary of Recommendations

First-Line

HR-positive

- Assessment of menopausal status is critical; ovarian suppression or ablation should be provided to patients who are premenopausal. Patients whose tumors express any level of hormone receptors should be offered hormone therapy. In Basic settings, if no immunohistochemistry testing is available, clinicians may presume hormone receptor positivity and offer tamoxifen in most cases.
- For patients with HR-positive, HER2-negative MBC, when non-steroidal AIs and CDK4/6 inhibitors are not available, use hormonal therapy alone. For life-threatening disease, clinicians may use single-agent chemotherapy; surgery may be used in cases in need of “salvage mastectomies” and for local control.

Summary of Recommendations

First-Line

HR-positive (cont.)

- For patients with HR-positive, HER2-negative MBC who are premenopausal, ovarian suppression or ablation plus hormone therapy should be offered.
- Patients with HR-positive, HER2-negative MBC for whom chemotherapy is offered, should be prescribed single-agent chemotherapy rather than combination chemotherapy, although combination regimens may be offered for highly symptomatic or life-threatening disease.
- Patients with HR-positive MBC with disease progression on an endocrine agent who are postmenopausal may be offered treatment with either:
 - endocrine therapy with or without targeted therapy or
 - single-agent chemotherapy.

Summary of Recommendations

First-Line

HR-positive (cont.)

- Patients with HR-positive MBC who are premenopausal without prior hormone therapy may be offered treatment with:
 - Tamoxifen, or ovarian ablation or ovarian suppression alone, or sequential hormonal therapy, or non-steroidal AIs with ovarian ablation or ovarian suppression and CDK4/6 inhibitors in Enhanced settings.
 - Tamoxifen, or ovarian ablation or ovarian suppression with hormonal therapy in Limited settings.
 - Tamoxifen in Basic settings.

Summary of Recommendations

First-Line

HR-positive (cont.)

- Patients with HR-positive MBC with disease progression on an endocrine agent who are premenopausal may be offered treatment with:
 - Ovarian ablation or ovarian suppression with hormonal therapy or sequential hormone therapy in Enhanced settings.
 - Alternative hormone therapy or surgery in Limited settings.
 - Tamoxifen and bilateral oophorectomy in Basic settings.

Summary of Recommendations

First-Line

HER2-positive.

- HER2-targeted therapy is recommended for patients with HER2-positive advanced breast cancer, except for those with clinical congestive heart failure or significantly compromised left ventricular ejection fraction, who should be evaluated on a case-by-case basis.
- Trastuzumab, pertuzumab, and taxanes for first-line treatment are recommended. If pertuzumab isn't available, then clinicians may offer chemotherapy and trastuzumab in Enhanced settings. Chemotherapy may be offered in Limited settings.
- For patients with HER2-positive and HR-positive MBC, various HER2-targeted therapies and chemotherapy or endocrine therapy, or chemotherapy alone or endocrine therapy alone may be offered depending on availability of anti-HER2 therapies. See Table 5 in the guideline for special circumstances for this population.

Summary of Recommendations

First-Line

Triple-negative.

- Patients with triple-negative MBC that is known PD-L1-positive may be offered the addition of an immune checkpoint inhibitor to chemotherapy as first-line therapy in Enhanced settings; most patients with triple-negative MBC in Limited settings may be offered chemotherapy.
- Patients with triple-negative, PD-L1-negative MBC should be offered single-agent chemotherapy rather than combination chemotherapy as first-line treatment.
- For *BRCA1* or *BRCA2* mutation carriers with metastatic HR-negative, HER2-negative breast cancer, PARPi therapy may be offered in Enhanced settings.
- Patients with HR-positive MBC and known *BRCA* mutations and if PARPi therapy is not available, treatment options include hormonal therapy with or without ovarian ablation.

Summary of Recommendations

Second-Line

HR-positive.

- In Enhanced settings, recommendations depend on prior treatment, for example, with prior endocrine therapy, clinicians may offer second-line endocrine therapy with or without targeted therapy (e.g., CDK4/6 inhibitor or everolimus). In Limited settings with prior endocrine therapy, clinicians may offer second-line endocrine therapy if available, otherwise, they may offer chemotherapy.

Summary of Recommendations

Second-Line

HER2-positive.

- HER2-targeted therapy should be given based on prior therapy and hormone receptor status. Trastuzumab deruxtecan or alternate HER2-targeted therapy regimens may be offered as second-line treatment depending on availability. In Limited settings, chemotherapy may be offered (with trastuzumab, if available). In Basic settings, if a patient has received prior treatment and medical treatment and pathology aren't available and has symptoms, clinicians may offer primary surgery for palliative reasons, including local control. If a patient finished trastuzumab-based adjuvant treatment less than one year before recurrence, offer second-line options. If more than one year before recurrence, offer first-line options.

Summary of Recommendations

Second-Line

HER2-positive, BRCA1/2 mutations.

- Patients with HR-positive MBC with germline *BRCA1/2* mutations no longer benefiting from endocrine therapy may be offered a PARPi rather than chemotherapy; chemotherapy may be offered if a PARPi is not available.

Triple-negative.

- In second-line, with or without prior PD-L1 checkpoint inhibitors, clinicians may offer chemotherapy, if sacituzumab govitecan is unavailable.
- Patients with triple-negative MBC with germline *BRCA1/2* mutations previously treated with chemotherapy may be offered a PARPi rather than chemotherapy.

Summary of Recommendations

Third-Line

HER2-positive

- In the third-line setting, clinicians should offer other HER2-targeted therapy combinations. (For patients with HER2-positive, HR-positive MBC, offer hormonal therapy with or without trastuzumab).

Triple-negative.

- In the third-line setting, patients with triple-negative MBC may be eligible for PARPi (if germline *BRCA1/2* mutation status is known), if not available, then clinicians may offer chemotherapy and/or palliative care.

See Table 8 in the guideline for other third-line regimens.

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Discussion

Limitations of the Research and Future Directions

- There are limitations on the evidence to inform some of the recommendations, due to many factors, such as prioritization of patient care and limited funding and infrastructure for research in this subject.
- When the optimal standard treatments are not available, where there are accessible established regional cancer centers, physicians may refer patients to them, where they may have access.
- Important limitations include insufficient research conducted in resource-constrained settings, lack of conclusive information on primary and preventive screening, and lack of published data on metastatic breast cancer management adapted to resource-constrained settings.
- Expert recommendations for resource-constrained settings should account for differential access to chemotherapy across Basic and Limited resource settings.
- A shortage in human resources of trained oncologists has led to task-shifting with variation in skill sets among general practitioners, general surgeons, and oncologists able to manage patients with metastatic breast cancer.

Limitations of the Research and Future Directions

- There is a significant need to further metastatic breast cancer research in resource-constrained settings, considering issues of surgery and chemotherapy access, treatment efficacy, and cost-effectiveness.
- The paucity of cancer research in limited resource settings needs further investigation which can be achieved through collaborative research. The use of targeted therapy and immunotherapy for patients with metastatic breast cancer is actively under investigation and further guidelines will include updates.

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/resource-stratified-guidelines
- Patient information is available at www.cancer.net

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Abbreviations

- AI, aromatase inhibitor
- ASCO, American Society of Clinical Oncology
- CDK, cyclin-dependent kinase
- EBMC, Evidence Based Medicine Committee
- HER2, human epidermal growth factor receptor 2
- HR, hormone receptor
- JCO, Journal of Clinical Oncology
- MBC, metastatic breast cancer
- PARPi, poly(ADP-ribose) polymerase inhibitors
- PD-L1, programmed cell death ligand 1
- RSG, resource-stratified guideline

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