EUROPEAN JOURNAL OF CANCER 42 (2006) 2897–2908

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

Position Paper

Evidence-based treatment of metastatic breast cancer – 2006 recommendations by the AGO Breast Commission

Gunter von Minckwitz, for The Breast Commission of the German Gynaecological Oncology Working Group (AGO)* [1]

Spokesman of the AGO Breast Commission, Univ. Women's Hospital Frankfurt, German Breast Group, Schleussnerstr. 42, 63263 Neu-Isenburg, Germany

ARTICLE INFO

Article history:
Received 27 April 2006
Received in revised form
2 June 2006
Accepted 6 June 2006

Keywords:
Metastatic breast cancer
Guideline
Evidence-based recommendations
Chemotherapy
Endocrine therapy
Trastuzumab
Bisphosphonates
Bone metastasis
Visceral metastasis
CNS metastasis

ABSTRACT

The Breast Commission of the German Gynecological Oncology Working Group AGO revises in annual intervals their evidence-based recommendations on therapy of primary and advanced breast cancer. A purely scientific assessment of the most recent published literature according to standardized level of evidence and grade of recommendation is supplemented by a newly developed AGO recommendation system which constitutes an expert consensus considering also clinical relevance, feasibility, and compliance. It is an approach of providing readers with an additional assessment trying to help them to select the most appropriate treatment for the individual patient situation. In the following, an overview is given on the most important aspects in diagnosis and therapy of metastatic breast cancer. For detailed aspects, a comprehensive set of slides including a more complete bibliography may be accessed under www.ago-online.org.

1. Objective

The Breast Commission of the German Gynaecological Oncology Working Group AGO revises in annual intervals their evidence-based recommendations on therapy of primary and advanced breast cancer. A purely scientific assessment of the most recent published literature according to standardised level of evidence and grade of recommendation[1] is supplemented by a newly developed AGO recommendation system (Table 1) which constitutes an expert consensus considering also clinical relevance, feasibility, and compliance. It is an approach of providing readers with an additional assessment trying to help them to select the most appropriate treatment for the individual patient situation. In the following, an overview is given on the most important aspects in diagnosis and therapy of metastatic breast cancer. For detailed aspects,

* Tel.: +49 6102 7987410; fax: +49 6102 7987440.
E-mail address: minckwitz@germanbreastgroup.de.
[1] Members and collaborators are listed at the end of the report.
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doi:10.1016/j.ejca.2006.06.033

Table 1 – Definition of the grade of recommendation by the Breast Commission

++	This examination or therapeutic intervention is highly beneficial for the patient, can be recommended without any restrictions and should be carried out.
+	This examination or therapeutic intervention is of restricted benefit for the patient and can be carried out.
+/–	This examination or therapeutic intervention has not shown any benefit so far and may be carried out in single cases. Due to the data basis, no explicit recommendation can be given.
–	This examination or therapeutic intervention may be detrimental to the patient and should therefore not be carried out.
– –	This examination or therapeutic intervention is detrimental and should by no means be carried out/i.e. should be refrained from.

a comprehensive set of slides, including a more complete bibliography, may be accessed under www.ago-online.org.

2. Procedure

Alternating every year, AGO commission members prepare presentations on the most important aspects of metastatic (and early) breast cancer management. For this purpose, a literature search of the Medline database as well as the abstract books of the last 5 years on the ASCO, ECCO, San Antonio Breast Cancer Symposium, and the European Breast Cancer Conference is performed. Subsequently, the experts suggest amendments to the guidelines slides of previous versions or preparation of new slides. At the beginning of every year, the suggestions for changes and amendments are presented and discussed in detail in the presence of all AGO Breast Commission members at a 3-day workshop. The final AGO recommendation grade for each statement is determined by simple majority each time, and it thus represents an expert consensus. Editorial corrections are subsequently made by the spokesman of the commission and the final guideline slide set is subsequently released by all members. The most recent version of the guideline slide set was issued in May 2006.

2.1. *Treatment strategy and objectives*

Metastatic breast cancer still has to be regarded as an incurable disease by treatment modalities available today. However, due to improved therapy options, patients show more often a chronic undulating course, which should be taken into account for the individual therapeutic management. Frequently the motto 'as little as necessary' might thus be more appropriate than 'as much as possible'.

Traditional objectives of palliative therapy are on the short term relief of tumour-induced pain and on the long-term preservation of physical activity resulting in a reasonable quality of life. More than ten recent phase-III studies demonstrated a significant prolongation of survival with patient numbers and study design suggesting high validity (LOE 1b). In addition, retrospective longitudinal observations observed a continuous prolongation of survival over several decades (LOE 2a). Therefore, treatment of patients with metastatic breast cancer today also aims at long-term prolongation of life and not just at palliation of symptoms. Two reasons with possible synergistic effects are currently under discussion for this improvement in prognosis: More effective drugs and combinations, especially when they are used as first-line therapy, and the increasing overall number of drugs that can be used sequentially throughout the course of disease.

Systemic therapy is of prime importance for treatment of metastatic breast cancer. Endocrine therapy appears to be the therapy of choice in patients with a hormone receptor positive tumour due a favourable risk (for toxicity)-benefit ratio (referred to therapeutic index) (LOE 1a, GR A, AGO++).[2,3] Chemotherapy has to be considered in patients with an immediate need for remission. Mono-chemotherapy appears to be in many cases more favourable in terms of treatment efficacy, toxicity profile, and quality of life. It is therefore indicated when the disease shows a slow, not life-threatening progression or if endocrine treatment is predicted ineffective due to low or absent steroid receptor status or exhausted after various treatment lines. Polychemotherapy usually provides higher efficacy at short term with a more unfavourable toxicity profile and impairment of quality of life. The therapeutic index therefore appears more advantageous in the case of foudroyant tumour progression with an imminent danger of organ failure or presence of severe tumour symptoms significantly impairing quality of life. Loco-regional intervention such as radiotherapy and operations is indicated for specific situations dependent on symptoms, metastasis pattern, and general condition of the patient.

2.2. *Prediction and monitoring of treatment effect*

The probability of treatment success in the metastatic situation can be assessed by means of the following predictors[4]:

- positive hormone receptor test in the primary tumour or metastasis for endocrine therapy (LOE 1a, GR A, AGO ++),
- response to 1st line endocrine therapy for a 2nd line endocrine therapy (LOE 1b, GR A, AGO ++),
- response to previous chemotherapy for next chemotherapy (AGO 1b, GR A, ++),
- presence of bone metastasis for the use of bisphosphonates (LOE 1a, GR A, AGO ++),
- amplification/over-expression of HER2 in the primary tumour or even better in metastasis tissue for trastuzumab (LOE 1a, GR A, AGO ++),
- premenopausal status for suppression of ovarian function and postmenopausal status for treatment with aromatase inhibitors (LOE 1c, GR A, AGO ++).

HER2 status should not be routinely used for selection of specific conventional therapies (anthracyclines, taxanes, tamoxifen, aromatase inhibitors) (LOE 2b-5, GR C-D, AGO +/–). This also holds true for measuring HER2 shed antigen (LOE 2b, GR C, AGO +/–)[5] and for detection of circulating tumour cells in blood (LOE 1b, GR B, AGO +/–).[6]