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Adjuvant Chemotherapy in Primary Breast Cancer

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Key Words
Chemotherapy, adjuvant · AGO · Anthracyclines · Breast cancer, early · Taxanes

Summary
Adjuvant systemic chemotherapy reduces the risk of relapse by about 25%. In hormone receptor-negative tumors, adjuvant chemotherapy is considered standard, independent of age or lymph node status. In hormone receptor-positive disease, an indication for adjuvant chemotherapy is given in patients at increased risk of relapse. Endocrine therapy should then be administered sequentially after chemotherapy. Anthracyclines are considered standard adjuvant therapy – superiority versus CMF (cyclophosphamide, methotrexate, 5-fluorouracil) was only demonstrated for anthracycline-containing polychemotherapy with 3 or more substances or for an anthracycline-CMF sequence. Several studies consistently indicate that addition of taxanes (docetaxel, paclitaxel) to anthracycline-containg chemotherapy results in a significant survival advantage. Since these data are so far only available for node-positive disease, taxanes should be an essential part of adjuvant chemotherapy in node-positive patients. Dose-dense chemotherapy is a valid option for node-positive patients, in particular for those with 10 or more involved axillary lymph nodes. Evidence-based therapy recommendations can be found in the annually updated guidelines of the AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) breast cancer commission.

Schlüsselwörter
Chemotherapie, adjuvante · AGO · Anthrazykline · Mammakarzinom, frühes · Taxane

Zusammenfassung
Adjuvante Chemotherapie reduziert das relative Rezidivrisiko um etwa 25%. Bei hormonrezeptor-negativem Tumor gilt die Chemotherapie unabhängig von Alter oder Lymphknotenstatus als adjuvante Standardbehandlung. Bei hormonrezeptor-positivem Tumor wird die Indikation in Abhängigkeit vom individuellen Rezidivrisiko gestellt. Die endokrine Therapie sollte dann sequentiell im Anschluss an die Chemotherapie durchgeführt werden. Als adjuvante Standard-Chemotherapie gelten Anthrazykline. Eine Überlegenheit gegenüber CMF (Cyclophosphamid, Methotrexat, 5-Fluorouracil) konnte bisher nur für anthrazyklinhaltige Polychemotherapien mit mindestens 3 Substanzen oder für eine Anthrazyklin-CMF-Sequenz gezeigt werden. Durch Taxane (Docetaxel, Paclitaxel) kann zusätzlich zu anthrazyklinhaltigen Schemata eine signifikante Überlebensverbesserung erreicht werden. Eine einheitliche Datenlage zu anthrazyklin-taxanhaltigen Schemata gibt es ausschließlich beim nodalpositiven Mammakarzinom – hier sollten daher Taxane Bestandteil der adjuvanten Therapie sein. Dosisdichte Chemotherapie ist eine Option für nodalpositive Patieninnen, insbesondere für Hochrisikopatientinnen mit 10 und mehr befallenen axillären Lymphknoten. Aktuelle, evidenzbasierte Therapieempfehlungen finden sich in der jährlich aktualisierten Leitlinie der AGO (Arbeitsgemeinschaft Gynäkologische Onkologie), Organkommission «Mamma».

*As members of the Breast Commission, part of the AGO (Working Group Gynecologic Oncology, German Society of Obstetrics and Gynecology)

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Introduction

In hormone receptor-negative tumors, adjuvant chemotherapy is considered standard, independent of age or lymph node status. In hormone receptor-positive disease, an indication for adjuvant chemotherapy is given in patients at increased risk of relapse. Endocrine therapy should then be administered sequentially after chemotherapy. Adjuvant chemotherapy should be started as soon as possible after definitive surgery and be completed before adjuvant radiotherapy.
Evidence-based therapy recommendations can be found in the annually updated guidelines of the AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) breast cancer commission [1].

Anthracyclines

Anthracyclin-containing combination therapy is considered standard in the adjuvant setting (fig. 1) [2]. The Oxford meta-analysis 2000 [3] shows an absolute decrease of about 4% in the 10-year risk of relapse and mortality in favor of anthracyclines compared to CMF (cyclophosphamide, methotrexate, 5-fluorouracil). The minimum dose for epirubicin (E) is ≥ 30 mg/m^2/week and ≥ 20 mg/m^2/week for adriamycin (A), respectively. In single studies, a significant advantage for anthracyclines compared to CMF has only been shown for anthracycline-containing polychemotherapies with 3 or more substances (e.g. $FE_{120}C$ or $FE_{100}C$) [4] or for an anthracycline-CMF sequence [5]. 4 cycles of $A_{60}C$ (or 4 cycles of $E_{90}C$) are considered equally effective as classical CMF with regard to survival (NSABP B-15) [6].
Neither increase in dose nor in number of cycles leads to a significant increase in survival for an anthracycline-containing 2-drug combination, not even when compared to CMF [7, 8]. In choosing the adequate chemotherapy protocol, one should keep in mind that the equieffectivity for CMF and 4 × AC has only been demonstrated for 'classical' CMF with 6 cycles (days 1 and 8) and oral cyclophosphamide (100 mg orally) on days 1–14. Dose reduction or prolongation of therapy-free intervals, e.g. in concurrent or 'sandwich' administration of CMF and radiation therapy [9], do severely endanger the therapeutic success of adjuvant chemotherapy [10]. In patients who should not receive anthracyclines due to pre-existing co-morbidities, adequately dosed CMF or 4 × TC (docetaxel/cyclosphosphamide) [11] may be considered as alternative therapy options.

Taxanes

In node-positive breast cancer, recent study data (e.g. CALGB 9344, NSABP B-28, BCIRG 001, PACS 01) suggest that a significant survival advantage is achievable by addition

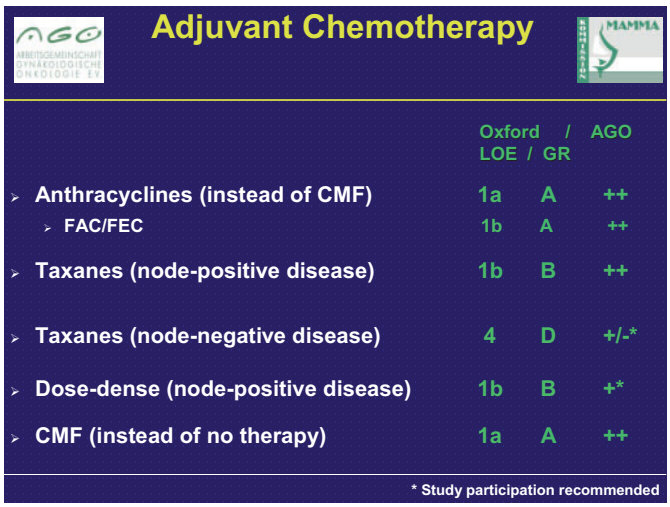

Fig. 1. Recommendations for adjuvant chemotherapy in primary breast cancer.

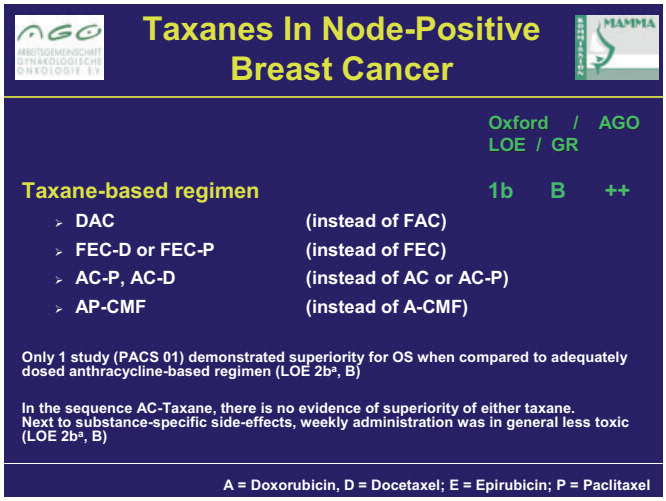

Fig. 2. Taxanes in the therapy of node-positive breast cancer.

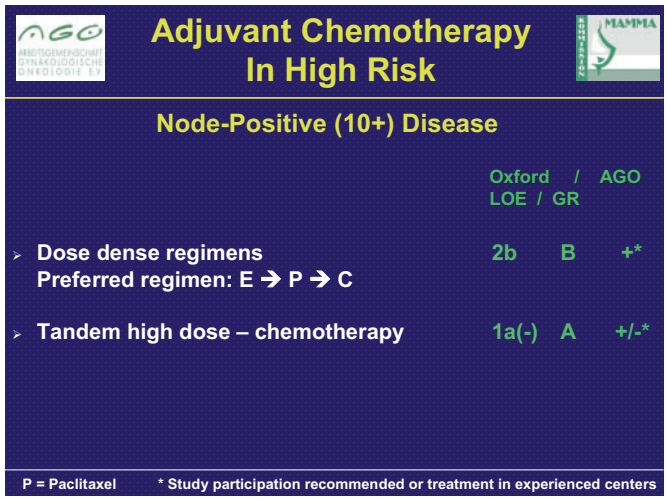

Fig. 3. Recommendations for adjuvant chemotherapy in node-positive patients, particularly with 10 or more positve axillary lymph nodes.

Table 1. Taxane-containing phase III adjuvant trials: results of taxane-containing experimental arm vs. anthracycline comparator

Trial (indication)	Trial design	Patients, n	Follow-up (median, months)	Results	Comments	Reference
CALGB 9344 (N+)	4×AC[a] vs. 4×AC[a] →4×P_{175} q21	3,121	68	positive	DFS + OS significantly better	Henderson et al. [8]
NSABP B-28 (N+)	4×$A_{60}C$ vs. 4×$A_{60}C$ → 4×P_{175} q21	3,060	65	DFS positive	OS n.s.	Mamounas et al. [16]
BCIRG 001 (N+)	6×$F_{500}A_{50}C_{500}$ vs. 6×$D75A_{50}C_{500}$ q21	1,491	55	positive	DFS + OS significantly better	Martin et al. [17]
PACS 01 Trial (N+)	6×$FE_{900}C$ vs. 3×$FE_{900}C$ → 3×D q21	1,999	60	positive	DFS + OS significantly better	Roche et al. [18]
MDA (N–/N+)b	6×$F_{50}A_{50}C_{500}$ vs. 4×P_{250} → 4×FAC q21	524	60	negative	insufficient statistical power	Buzdar et al. [19]
GEICAM 9906 (N+)	6×$FE_{90}C$ q21 vs. 4×$FE_{90}C$ q21 → 8×P_{100} q7	1,248	46	DFS positive	OS n.s.	Martin et al. [20]
US Oncology (N0/N+)	4×$A_{60}C$ vs. 4×$D_{75}C$ q21	1,016	66	DFS positive	OS n.s.	Jones et al. [11]
E2197 (N0/N+)	4×$A_{60}C$ vs. 4×$A_{60}D_{60}$ q21	2,778	53	negative	DFS + OS n.s.	Goldstein et al. [21]

[a]AC was evaluated in 3 different doses: 60 vs. 75 vs. 90 mg/m^2.
[b]33% neoadjuvant therapy.
A = Adriamycin; C = cyclophosphamide; F = 5-fluorouracil; E = epirubicin; D = docetaxel; P = paclitaxel; q21 = every 21 days; q7 = every 7 days; DFS = disease-free survival; OS = overall survival; n.s. = not significant.

of taxanes (paclitaxel, docetaxel) to adjuvant anthracycline-containing chemotherapy (table 1). These data suggest anthracycline/taxane-containing regimens (e.g. 4 × AC/EC → 4 × paclitaxel; 6 × TAC; 3 × FEC → 3 × docetaxel) to be suitable as standard therapies in node-positive patients (fig. 2). Whether adequately dosed anthracyclines and taxanes are administered in combination or as sequential regimens does not seem to impact patient outcome. Use of dose-dense, growth factor-supported anthracycline-, taxane- (paclitaxel) and cyclophosphamide-containing chemotherapies seems to be advantageous in node-positive disease according to the CALGB 9741 [12, 13] and AGO ETC [14] trials. These regimens are thus valid therapy options in node-positive patients, particularly in high-risk patients with 10 or more involved axillary lymph-nodes (fig. 3). Longer follow-up as well as results from currently ongoing studies will help to draw definite conclusions on whether dose-dense chemotherapy leads to permanent survival improvement and which patients derive particular benefit.

Data regarding anthracycline- and taxane-containing regimens in node-negative disease are still scarce and inconclusive. This indication is therefore evaluated in ongoing trials (e.g. NNBC-3, SUCCESS). Similarly, the impact of high-dose chemotherapy with stem cell support is still controversial, even though a recent trial showed a statistically significant survival advantage [15]. Control groups in published high-dose trials did not receive chemotherapy regimens that would be considered standard according to current guidelines. Therefore, high-dose chemotherapy should only be performed within clinical trials (fig. 3).

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