Is Chemoendocrine Treatment without Alternative?

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Introduction

Current trial-based evidence is insufficient for answering the questions asked in the debate of this volume of Breast Care: (i) The optimal type and duration of endocrine therapy is ill-defined in these comparisons in the premenopausal setting [1–3] and has significantly further developed in the postmenopausal setting in the recent past [1, 4, 5]. (ii) None of the chemotherapy regimens of the overview data presented in direct comparisons of chemoendocrine versus endocrine therapy alone would nowadays be considered standard since they lacked taxanes and might be less efficient [6]. In fact, taxanes provided similar benefit in estrogen receptor (ER)⁺ versus ER⁻ patients independent of lymph node status [7, 8]. In addition, suboptimal dose intensities below 85% of even cyclophosphamide/methotrexate/5-fluorouracil (CMF) [9] and the lack of sufficient rates of neutropenia-reduced outcomes of patients compared to endocrine therapy alone make fair comparisons of often suboptimal endocrine therapy with also suboptimal chemo(endocrine) therapy difficult [10]. (iii) The trials usually compared chemotherapy with endocrine therapy, but there is not sufficient data from trials comparing chemotherapy plus tamoxifen with luteinizing hormone-releasing hormone (LHRH) analogs plus tamoxifen and LHRH analogs alone [1]. (iv) The relevant trials testing optimized modern endocrine therapy ± adequate chemotherapy in premenopausal patients like BIG 4–02 (Perche) and Promise have been closed prematurely due to slow patient recruitment.

Indirect comparison clearly points to the existence of patient populations that may be overtreated by chemoendocrine therapy [6], but until further elucidation by the risk-adapted approaches tested in the TAILORX and the MINDACT trials, only indirect comparisons of pros and cons will be possible for a long period of time.

Premenopausal Patients

What Can We Achieve with Endocrine Therapy alone and Do Really All Patients Benefit from Additional Chemotherapy?

Low-Risk Patients

Tamoxifen is the standard component of any endocrine therapy in premenopausal women, but its efficacy increases when combined with oophorectomy or hormonal ablation via LHRH analogs, independent of whether it is used as the only treatment [11] or as an adjunct to a prior chemotherapy [12]. By combining tamoxifen with oophorectomy, excellent results with 97.5% 5-year overall survival (OS) have been obtained in patients with a tumor size < 3 cm, node negativity and proven ER expression [11]. Recent combination trials nearly exclusively use LHRH analogs instead of oophorectomy, although the latter may be superior due to its longer and irreversible action [1, 6]. Prolonged administration for 5 years has therefore been recommended by consensus meetings for patients with high-risk features like axillary nodes, Her2/neu expression and/or very young age [13]. Despite these limitations, treatment with LHRH analogs plus tamoxifen versus anastrozole in the ABCSG 12 trial recently demonstrated a 5-year disease-free survival (DFS) and an OS of 92.4 and 98.7%, respectively, in a population of premenopausal patients comprising 70% low- and 30% intermediate-risk patients with lymph node involvement [14]. It may be safe to state that for the group of lowest-risk patients with high expression of hormone receptors (HRs), node negativity and low tumor size as well as simultaneous absence of other risk factors, combined endocrine therapy is an excellent treatment. It is hard to imagine that *for the total group of low-risk patients* a general approach with additional chemotherapy would be justified or would add any other than the risk of acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) [15], particularly in granulocyte

colony-stimulating factor-supported dose-dense or intense trials [16]. In support of such a view, subgroup analyses of trials randomizing goserelin to CMF favored by trend goserelin in patients of <40 years and with tumors of <2 cm, grade 1/2, and with expression of both receptors [17]. Future research will have to follow a strategy where the acute and long-term burden of treatment is deescalated in the lowest-risk patients, e.g. by avoidance of chemotherapy but inclusion of novel agents, as successfully exemplified by the addition of zoledronic acid in the ABCSG 12 trial [14]. Further incorporation of biologicals in such treatment regimens will be an interesting research option in the future.

Lymph Node-Positive Patients

The data of ABCSG 12 and other trials point to the existence of subpopulations of ER⁺ lymph node-positive patients that may be overtreated by a chemoendocrine approach. However, it must be kept in mind that many endocrine-alone trials combined low- and intermediate-risk patients although their prognosis differs significantly and although tamoxifen plus hormonal ablation cannot overcome the intrinsic risk of positive nodes, pathologic tumor size and grade-3 histology [18]. The 5-year DFS and OS for a population comprising nearly 50% of patients with involved nodes were only 74 and 78% [18] in patients treated with tamoxifen plus oophorectomy and, accordingly, the 10-year OS was only 76% in a population of patients with 100% lymph node involvement treated with LHRH analoga, tamoxifen and chemotherapy [12], thus leaving ample space for improvement. In addition, lymph node-positive patients may fare worse with endocrine therapy alone as compared to chemotherapy [19]. Conclusions from the majority of low-risk patients in trials with mixed populations must therefore be drawn with caution and risk/benefit ratios must be calculated differently for lymph node-positive patients, particularly in the light of results with modern treatment approaches [8].

In this regard, the CALGB and the US Breast Cancer Intergroup recently reported on the results obtained by three modern chemotherapy regimes (two including taxanes) in the subgroups of lymph node⁺ ER⁺ versus ER⁻ patients [20]. The main effect in risk reduction for early relapse and survival in the ER⁺ subgroup was obtained by tamoxifen, and although taxane-containing chemotherapy reduced the relapse rate numerically, this was not statistically significant. This reduction in risk after 3 years apparently occurred independently of the degree of lymph node involvement and tumor size. In addition, this trial demonstrated that women younger than 50 years did not benefit from extensive or intensive chemotherapy regimens. However, it has to be stated that the trial results are in overt contrast to the data from taxane meta-analyses which demonstrate benefit from taxanes independent of ER status, number of nodes involved and menopausal status [8].

Thus, although the group of patients sufficiently treated by an endocrine approach alone may be larger than usually antici-

pated, the tools for the adequate identification must still be developed. Adjuvant online!, though a helpful tool, underestimates the true risk of an event particularly in patients < 35 years and in those with lymphovascular invasion by almost 14 and 4%, respectively [21]. The need to individualize risk estimation is supported by data of the IBCSG VIII trial comparing CMF followed by goserelin with either treatment alone in which chemoendocrine treatment was superior over endocrine treatment over a wide range of ER expression (50–75%), with an approximation of the 5-year DFS curves only in the range of 90% ER expression and beyond [22]. In addition, patients with absence of progesterone receptor (PgR) expression [22] and those < 35 or 40 years old clearly benefitted from combination therapy [12, 23]. It also has to be stated that patients with ER⁺ tumors overexpressing Her2/neu or with amplified Her2/neu derived benefit from high-dose cyclophosphamide/doxorubicin (adriamycin)/5-fluorouracil (CAF) in CALGB study 8541 and, until further information, should be treated with an adequate chemoendocrine plus Her2/neu-targeting approach.

Her2/Neu Expression and Histologies Other than Invasive Ductal Cancers

In the latest St. Gallen vote, about 50% of participants voted for the combination of endocrine therapy and trastuzumab in < T1c, lymph node-negative, ER⁺ tumors, and in a pattern of care study in 2007 the majority of oncologists was uncertain about or rejected chemoimmunotherapy [24]. Both approaches are without any evidence, and an endocrine-alone treatment might be justified in this lowest-risk population even in the presence of Her2/neu, particularly considering the potential long-term risks of anthracyclines and trastuzumab.

Lobular invasive breast cancers are often HR⁺ and have a better prognosis, although adjuvant endocrine treatment may be less efficient as compared to invasive ductal cancers [25]. Yet, in retrospective reviews, patients had the identical outcome to invasive ductal cancers despite more classical unfavorable features and a lower rate of adjuvant treatment [26]. Given the lower chemosensitivity, the identical outcome despite larger size favors a more liberal use of an endocrine-only approach and a lesser weighing of size in these patients. This also seems justified.

Wish for Reproduction: Long-Term Menopause Induction by Chemotherapy versus Endocrine Therapy

In uncontrolled trials, LHRH analoga have shown a protective effect against chemotherapy-induced menopause in young women with the wish for preservation of fertility [27]. Given the efficacy of LHRH analoga in reducing cancer relapse, the sole administration of this drug was accepted in the St. Gallen recommendations as a treatment alternative in patients who want to preserve their fertility, and ovarian ablation was considered an option in high-risk and/or BRCA mutation carriers in this regard.

Comorbidities

The presence of comorbidities like myelodysplastic syndromes, relevant cardiovascular disorders, neuropathies or myopathies, which might deteriorate during chemotherapy or significantly increase the risk of treatment-associated life-threatening complications, may favor the use of endocrine treatment alone. Particularly in the presence of severe comorbidities, the risk profile included in such an approach may be more liberal and may also comprise patients with involved lymph nodes.

Postmenopausal Patients

Patients should not be discriminated for age regarding the receipt of the optimal type of therapy and should receive benefit from chemotherapy independent of age between 50 and 69 [28] and even 70 years and older [29]. This has led to the elimination of specific recommendations for elderly subsets of breast cancer patients in the St. Gallen guidelines [30], and an increasing use of chemotherapy in older women in the USA including the application of taxane-containing regimens [29], which seems justified by the meta-analysis data. In fact, even 66% of patients aged 70–80 years with lymph node-positive ER^{-ve} disease received chemotherapy in this analysis. However, even in patients with 1–3 lymph nodes involved, anthracycline-containing chemoendocrine therapy yielded a DFS benefit only after 9 years without any survival difference at that time [31] and Southwest Oncology Group (SWOG) patients in a similarly designed trial experienced a survival advantage only after 10 years [32].

In the Surveillance, Epidemiology and End Results (SEER) population of 41,390 patients mentioned above [29], however, postmenopausal patients with ER^{+ve} disease did not receive benefit from chemotherapy in terms of breast cancer survival and OS, and this was true for the lymph node-negative as well as for the lymph node-positive subsets [29]. These data mean an essential caveat against the overuse of chemotherapy in endocrine-responsive postmenopausal low- to intermediate-risk breast cancer patients. In addition, it has to be stated that in some of the trials included in the Oxford overview, the median time for tamoxifen treatment was suboptimal [33], that modern endocrine therapy definitely includes aromatase inhibitors, thereby further increasing the benefit of ER^{+ve} patients [4, 5], and that even prolonged application of aromatase inhibitors further reduces relapse risks and even mortality in some HR^{+ve} patients [34, 35]. It is also emerging at the horizon that polymorphisms in cytochrome P450 [36] as well as the deliberate use of selective serotonin reuptake inhibitors (SSRIs) and other drugs might substantially modify the efficacy of tamoxifen, thus leading to suboptimal exploitation of its benefits in the past. While it might be argued that any such additional benefit might also be present for patients receiving chemoendocrine therapy, the additional benefit by chemotherapy

added to the basic efficacy of optimized hormonal therapy could shrink significantly in the future for well-defined patients. While the long-term effect of a short application of chemotherapy on cancer stem cell biology, cytokeratine-positive dormant cells in the bone marrow or premalignant cells in the residual breast remains to be defined, this might be better achieved with tools targeting the microenvironment and endocrine therapy in patients in whom the early risk of relapse is not a threat. If such a strategy proves successful in low- and intermediate-risk patients in the future, the proportion requiring chemotherapy could further decrease.

Taken together, endocrine therapy alone may be the treatment of choice in frail patients, in some selected low- to intermediate-risk patients with a life expectancy below 5 and 10 years, which is the time frame for differences in relapse-free survival (RFS) and OS to emerge from additional chemotherapy, respectively. A high probability of compliance, the presence of contraindications for chemotherapy and the absence of contraindications against endocrine therapy may support such a decision. In any way, these decisions require careful consideration and extensive discussion of pros and cons and the patients' informed consent.

Tools for a More Precise Risk Determination and Individual Tailoring of Chemoendocrine versus Endocrine Treatment

Biomarker-Driven Selection of Treatment (TAILORIX and MINDACT)

The proliferative potential of breast cancer cells is well known for its predictive power for relapse and death [37]. Ki67 contributes to the predictive power of the Oncotype DX 21 gene array [38], possibly differentiating for the need of endocrine versus chemoendocrine treatment in low-risk patients [39] and under phase-III testing at present. However, in the IBCSG VIII and IX trials, responses to chemoendocrine versus endocrine therapy did not differ over the full range of Ki67 expression observed [40]. Independent of other prognostic factors, ONCOTYPE DX predicted the definite need for and gain by additional chemotherapy in a subset of lymph node^{-ve} ER^{+ve} tumors, thus clearly underlining the prognostic heterogeneity of this group of patients [39]. Not surprising clinical need, not scientific evidence are fostering the broad introduction of gene arrays like ONCOTYPE DX and Mammprint in the US market even prior to the readout of phase III trials like TAILORIX and MINDACT [24, 41].

Predefining Endocrine and Chemotherapy Sensitivity

Gene signatures are under evaluation that predict resistance to adjuvant tamoxifen [42] or sensitivity to chemotherapy [43] and might become useful for the discrimination of patients benefitting from chemo- instead of endocrine therapy or requiring additional chemotherapy. Attempts to identify incom-

pliant subsets of patients in advance and to increase the remarkably low compliance of patients with endocrine treatment are under way [44] and may help in defining patients better off with endocrine therapy alone or requiring chemotherapy, and in increasing the net effect of endocrine-alone treatments.

Until these novel tools enter real-world scenarios, decision-making processes will require careful consideration of scientifically complex constellations, the integration of the patients' wishes on the basis of informed consent, and the recruitment of patients in well-designed studies suitable for clarifying these urgent questions.

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