EC-Doc was strongly superior to FEC in HER2+ tumors (HR=0.29, 95% CI: 0.12-0.7, p=0.006) but not in HER2- tumors (p=0.18). In Topo-II aberrated tumors, the benefit of EC-Doc was remarkably strong (HR=0.28, 95% CI: 0.11-0.69, p=0.006), whereas the benefit was not significant in Topo-II normal tumors (p=0.16). Figure 3: DFS in EC-Doc vs. FEC according to HER2 negative and positive tumors.

Abstract

Background: Despite extensive research, there is still no consensus on optimal predictors for use of taxane-based chemotherapy (taxo) in early breast cancer. Some studies have revealed HER2 as a significant predictive marker for efficacy of taxanes and anthracyclines. TIMP-1 and Topo-II are reported to be predictive for anthracycline efficacy. In our previous reports, both KI-67>20% and central G3 status emerged as significant predictors for taxo benefit. We have now compared HER2 and Topo-II (as protein expression and gene amplification) and TIMP-1 immunoreactivity as well as factor combination (HT [HER2/TIMP-1] 1 and 2) (Topo-II/HT) regarding their predictive value for benefit from taxo-based cht.

Methods: The EC-Doc trial randomized 1950 patients with 1-3 positive LN to EC/9F/Cm or 4xEC-4xDoc. Significantly better DFS and OS favoring EC-Doc have been previously reported (Nitz et al, SABCS 2008). Protein expression and gene amplification data as well as central histology/grade were available for 772 patients. Survival analysis was performed using Cox proportional hazards and Kaplan-Meier statistics. Analysis of HER2 survival impact status was prospectively planned.

Results: The entire and the investigated study populations did not differ regarding baseline characteristics. After median follow up of 64 months, both DFS (by 95% vs. 80%, p=0.006) and OS (by 95% vs. 92%, p=0.022) rates significantly favored EC-Doc over FEC in this cohort as well. HER2 over-expression (3+ and/or FISH>2.0) was reported in 158 tumors (20%). Topo-II aberration (deletion or amplification) was reported in 78 (49.4%) HER2+ and in 83 (13.6%) HER2-negative tumors. 496 tumors were classified as TIMP-1 immunoreactive (65.2%). None of these factors were significantly prognostic for DFS in this collective. Regarding DFS, EC-Doc was strongly superior to FEC in HER2+ tumors (HR=0.29, 95% CI: 0.12-0.7, p=0.006) but not in HER2- tumors (p=0.18). In Topo-II aberrated tumors, the benefit of EC-Doc was remarkably strong (HR=0.28, 95% CI: 0.11-0.69, p=0.006), whereas the benefit was not significant in Topo-II normal tumors (p=0.16), which comprise more than ¾ of the total. In contrast, Topo-II protein overexpression (+10%) was not associated with a stronger benefit in either subgroup. The superiority of EC-Doc to FEC was significant in the larger group of TIMP-1 immunoreactive tumors (HR=0.57, p=0.025) but not in TIMP-1 negative tumors (p=0.14), similar behavior was seen in KI-67 and TIMP-1 subgroups (significant with HR about 0.5 in the “+” subgroups). In a multivariate model for DFS including age, tumor size, KI-67, grade, HR, HER2, TIMP-1 aberration, TIMP-1 status, therapy and interactions of all factors with therapy arm, the only significant therapy interaction was that of (high) KI-67 (HR=0.76, 95% CI: 0.59-0.98, p=0.03). All significant main effects in this model were age, central grade, and KI-67.

Conclusions: These data suggest predictive significance for Topo-II aberration, TIMP immunoreactivity and HER2 over-expression as well as multivariate predictive significance of high KI-67 for enhanced benefit of taxane-based cht.

Background

• Breast cancer (BC) patients with 1-3 positive lymph nodes belong to the intermediate risk group, and chemotherapy therapy (in HR+ disease) is current standard of care in all HR+ patients. Identification of BC markers in this subgroup with favorable outcome is urgently needed to prevent substantial overtreatment of 50-70%1

• Previous studies reported predictive effect of HER2+, topoisomerase II status2 and tissue metalloproteinase inhibitor 1 TIMP-1 status2 for efficacy of anthracyclines and taxanes.

• Aim of the study was to investigate these markers among other prognostic markers as prediction markers for taxo efficacy within the randomized cohort of intermediate risk patients.

Methods

• Treatment details are given in Figure 1.

• Primary tumor samples from all cases with either relapse or completed 5 years of follow up (in September 2009) were retrieved for the central tumor bank.

• Tumor samples from 772 patients (40% of the original study population) were included in the analysis

• Non-IT pts (n=81) and pts treated by CMF (due to marginal clinical impact on n=81) were excluded

• ER, PR were considered positive if moderate or strong immunostaining was seen in ≥ 1% of tumor nuclei. HER2 was considered positive if scored as 3+ according to HercepTest criteria. If 2+ Fisher had to show amplification (ratio ≥2.0), KI-67 was positive if nuclear staining was seen in ≥ 20% tumor cells

• Topo-II was considered as abnormal if deletion (>0%) or amplification (>2) was present within FISH analysis

• Topo-II protein expression was considered as positive if ≥10% of nuclei were stained as well as a measure of TIMP-1 immunoreactivity in the epithelial breast cancer cells

• HER2-negative and TIMP-1 immunoreactive tumors were classified as HT nonresponsive and otherwise HT responsive

• Tumors with normal TOP2A status and TIMP-1 immunoreactivity were classified as 2T-nonresponsive and otherwise 2T-responsive.

• Statistical analysis used the Kaplan-Meier method to estimate cumulative survival time probabilities. The log-rank test (p<0.05) was applied to test for survival difference according to treatment. Univariate Cox analysis for DFS was performed for each individual tumor, together with treatment, prog markers with significant univariate results were entered into multivariate forward stepwise Cox regression analysis for DFS.

Results

• Baseline characteristics were similar between the tumor bank (n=772) and the entire study population (n=1950).

• Median age was 52 years, median tumor size 2.1 cm, 46% of patients had 1 positive lymph node

• After median follow up of 64 months, event-free survival was superior in both the whole study population (data submitted for publication) and the tumor bank subgroup (5 year DFS EC-Doc vs. FEC 95% vs. 80%, p=0.006) (Figure 2).

• The randomized collective with intermediate risk BC.

• Univariate prognostic analysis: Only Ki-67 overexpression, central G3, young age of patients (<50 years old) and negative HR status were significant predictors for survival

• Central grade was distributed as follows: 0:120 (n=334), 1:285 (63.4%) and 2:315 (66.6%).

• HER2 over-expression (3+ and/or FISH>2.0) was reported in 158 tumors (20%). Positive correlations are reported between positive HER2 status and Ki-67 overexpression (r=0.215, p=0.001), poor grade (r=0.223, p=0.001) and Topo-II aberration (s. below)

• Topo-II aberration (57%) and HER2 status (83%) were determined.

• 158 tumors were classified as TIMP-1 immunoreactive (65.2%). No significant correlations between TIMP-1 immunoreactivity and other markers, grade, Ki-67, HER2, Topo-II status were determined.

• 362 tumors were classified as HT responsive (47.6%) and 598 as HT non-responsive (52.4%)

• The overall and the investigated study populations did not differ regarding baseline characteristics. After median follow up of 64 months, event-free survival was superior in both the whole study population (data submitted for publication) and the tumor bank subgroup (5 year DFS EC-Doc vs. FEC 95% vs. 80%, p=0.006) (Figure 2).

• Figure 1. Design of the study

• Figure 2. Event-free survival by treatment arm

Conclusions

• HER-2, Topo-II aberration and nominally TIMP-1 are shown as significant predictive factors for taxo benefit in the randomized collective with intermediate risk BC.

• However, the predictive effect of HER2 and Topo-II seem to be related to the proliferative effects of these markers, as shown by multivariate interaction analysis

References


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