Methods

DRP algorithm

The DRP algorithm is based on cell line data from National Cancer Institute, NCI60 (5). Gene expression data from cell lines is correlated to the sensitivity pattern (measured as GI50 values) to epirubicin showing which genes are correlated to sensitivity and which genes are correlated to resistance. To select the clinical relevant pathways, gene expression from more than 3000 patients tumors of different origin are compared to the raw DRP. Gene expression that are not taking part of any meaningful biological pathway in the 3000 tumors are excluded from the final DRP.

Epirubicin sensitivity predictor

Among 716 consecutive patients with advanced breast cancer from a DBCG cohort, 135 patients were treated with epirubicin at any treatment line between May 1997 and November 2015 at one of the ten participating sites. See baseline characteristics in Table 2. Patients were examined every 9 to 12 weeks by CT scan and clinical evaluation. After patient informed consent, mRNA was isolated from formalin fixed paraffin embedded tumor tissue from diagnostic biopsies and analyzed using Affymetrix arrays. Analysis of epirubicin efficacy were compared to clinical data collected retrospectively from patients’ medical and pathological records. Statistical analysis was done using Cox proportional hazards model adjusted for treatment line. Primary endpoint was time to progression (TTP).

Results

Median time to progression was 9.9 months (95% CI: 7.2–13.2). Of the 135 patients, four received epirubicin more than once. Scoring the DRP as a continuous covariate demonstrated that the DRP was significantly associated to TTP (p = 0.03) by comparing two patients with DRP scores differing by 50 percentage points the hazard ratio was 0.54 (95% CI: 0.35–0.82) suggesting an even stronger separation in the risk between extreme DRP values.

Conclusion

The current study demonstrates a potential clinical value by being able to select patients that benefit from epirubicin against patients predicted not to benefit sparing the last patients unnecessary toxicity.

Abbreviations:
- AI: Aromatase Inhibitor
- AR: Aromatase Receptor
- ASBO: Aromatase Inhibitor (Bosentan) study
- CRP: C-reactive protein
- DFS: Disease Free Survival
- DRP: Drug Response Predictor
- ECOG: Eastern Cooperative Oncology Group
- GI50: Growth Inhibition 50
- HR: Hazard Ratio
- HR2: Human Epidermal Growth Factor Receptor 2
- HER2: Human Epidermal Growth Factor Receptor 2
- HR3: Human Epidermal Growth Factor Receptor 3
- OR: Odds Ratio
- OS: Overall Survival
- PFS: Progression Free Survival
- TTP: Time to Progression