Benefit from anthracyclines in relation to biological profiles in early breast cancer

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Abstract There are no validated predictors of benefit from anthracyclines. We compared cyclophosphamide, methotrexate, 5-fluorouracil (CMF), and epirubicin in different sequences with CMF alone in a phase III trial on operable breast cancers. Outcomes were analyzed in relation to tumor biological profiles to identify potential predictors of the efficacy of different treatments/drug combinations. Patients with N− or 1–3N+ tumors, were randomized to receive (a) epirubicin (4 cycles) followed by CMF (4 cycles); (b) CMF (4 cycles) followed by epirubicin (4 cycles), or (c) CMF (6 cycles) alone. Immunohistochemical assessments of estrogen (ER) and progesterone (PgR) receptors, HER2 and Ki67 were available for 705 patients (arm A/B/C: 276/269/160). Prognostic and predictive relevance was analyzed by log-rank tests and Cox models. Ki67 > 20 % and absent/low expression of ER and PgR were associated with worsen disease-free (DFS) and overall survival (OS). In patients with triple negative tumors (ER−, PgR−, HER2−), epirubicin-containing regimens yielded better DFS (HR 0.33, 95 % CI 0.17–0.62, $P = 0.0007$) and OS (HR 0.24, 95 % CI 0.10–0.57, $P = 0.001$) compared with CMF alone, whereas no differences were found in patients with HER2-positive (HER2+, ER−, PgR−) subtype. Treatment by subtype interaction (HER2-positive vs. others) was significant for DFS ($\chi^2 = 6.72$, $P = 0.009$). In triple unfavorable (ER−, PgR−, Ki67 > 20 %) tumors, the use of epirubicin yielded better DFS (HR 0.45,95 % CI 0.26–0.78, $P = 0.005$) and OS (HR 0.30, 95 % CI 0.15–0.63, $P = 0.001$). Epirubicin-containing regimens seem to be superior to CMF alone in patients with highly proliferating, triple negative or triple unfavorable tumors .