Title: The responsiveness of intrinsic subtypes to adjuvant anthracyclines versus non-anthracyclines in NCIC.CTG MA.5 randomized trial

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Background: Recent studies have suggested that intrinsic breast cancer subtypes may differ in their responsiveness to specific chemotherapy regimens. We assigned intrinsic subtypes to breast tumors from NCIC.CTG MA.5, a clinical trial that randomized node positive women to CMF (cyclophosphamide-methotrexate-5FU) vs. CEF (cyclophosphamide-epirubicin-5FU), and examined the differential response to adjuvant anthracycline chemotherapy.

Method: The intrinsic subtype was obtained from 476 tumors using the qRT-PCR PAM50 gene expression test.Tumors were classified into Luminal A, Luminal B, HER2-enriched (Her2-E), Basal-like and Normal, and correlated with relapse-free (RFS) and overall survival (OS). Survival was estimated using Kaplan-Meier plots and log-rank test. Multivariable Cox regression analyses were used to determine the significance of the interaction between treatment and intrinsic subtypes, adjusted withstandard clinicopathological variables.

Results: Intrinsic subtypes were significantly associated with RFS (p=0.0005) and OS (p<0.0001) on the entire cohort. The HER2-E subtype demonstrated the greatest benefit from CEF vs. CMF, with an absolute difference of more than 20% in both 5-yr RFS and OS, while there was a <2% difference for the non-HER2-E tumors (interaction p = 0.03 for RFS and 0.02 for OS). Within tumors defined clinically as Her2+ by immunohistochemistry or FISH, 79% (72/91) were classified as the HER2-E subtype by genomics and these tumors were also significantly associated with better response to CEF vs. CMF (62% vs. 22%, p = 0.0006). In contrast, Basal-like tumors (n = 94)did not benefit from the substitution of methotrexate for epirubucin with an HR of 1.1 for RFS and 1.3 for OS in favor of methotrexate but the test for interactionwas not significant.

Conclusion: Across the intrinsic subtypes, HER2-E assignment strongly predicted anthracycline-sensitivity; furthermore, the benefit of anthracyclines is greatest in tumors that are both clinically Her2+ and Her2-E. Strikingly, the chemotherapy-sensitive Basal-like tumors showed no benefit for CEF, suggesting that non-anthracycline regimens should be further investigated in this subtype.