SIGNIFICANCE OF BREAST CANCER SUBTYPES APPROXIMATED BY HORMONAL RECEPTOR STATUS AND HER-2 STATUS IN LOCALLY ADVANCED BREAST CANCER PATIENTS

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INTRODUCTION: Breast cancer is a clinically heterogeneous disease driven by the genetic variability of patients and tumors. Intrinsic subtype predictor is a novel molecular classification of breast cancer based on large-scale gene expression analyses of breast cancer. There are four major molecular classes of breast cancer; luminal-A, luminal-B, basal-like and human epidermal growth factor receptor (HER-2)-positive breast cancer. The overall survival and chemotherapy sensitivity of the different molecular subgroups vary. The studies have proved that luminal-type cancers have more favorable long-term survival, whereas basal-like and HER-2 are more sensitive to chemotherapy. However, most of the studies based on the molecular subtypes identified by microarrays analysis which is practically inaccessible for its expensiveness.

BACKGROUND: According to treatment guidelines issued by the National Institutes of Health (NIH) Consensus Statement on Adjuvant Therapy in Breast Cancer and the St. Gallen Consensus Statement, the current standard for prognostic stratification includes multivariate prediction models. Although these tools integrate multiple conventional clinicopathological parameters, they only address the potential benefit of adjuvant therapy for groups of patients with given disease characteristics but not for an individual patient. Therefore, more accurate molecular prognostic and response prediction tools like intrinsic subtype predictor were proposed to introduce more individualized treatment. However, gene expression profiling is impractical for the time and expense required. Therefore, some studies have proposed to use readily available clinical receptors to approximate breast cancer subtypes. The studies have shown similar prognostic effect of breast cancer subtypes approximated by hormonal receptor and HER-2 status like intrinsic subtypes identified by microarrays analysis.

PURPOSE: The aim of this study was to determine the prognostic significance of breast cancer subtypes approximated by hormonal receptor status and HER-2 status in locally advanced breast cancer patients treated with primary systemic treatment.

METHODS: Fifty one patients with AJCC stages IIB, IIIA, IIIB or inflammatory breast cancer who received primary systemic treatment in N.N.Blokhin Russian Cancer Research Center, Moscow from 2004 to 2008 were included. In primary systemic setting, 32 patients (62.8%) were treated with cyclophosmide, doxorubicin and 5-fluorouracil (CAF), 6 (11.4%) with taxane-based regimens and 13 (25.4%) with other taxane-based regimens including Herceptin, Avastin. Standard surgical procedure was modified radical mastectomy. HR-positive patients received adjuvant endocrine therapy. Breast cancer subtypes were classified as Luminal A (ER+ or PR+ and HER2-), luminal B (ER+ or PR+ and HER2+), HER-2(ER- and PR- and HER2+), and basal (ER- and PR- and HER2-). Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death/

last date known to be alive. Disease-free survival (DFS) was defined according to the Manual of the European Organization of Research and Treatment of Cancer as the interval between the date of surgery, or in patients with pathological complete response, the date on which complete clinical response was achieved, and the date of first evidence of recurrence. Both rates were estimated by the Kaplan-Meier method. Cox proportional hazard regression model was applied for univariate analysis.
RESULTS: Regarding progression free survival (PFS), luminal A had significantly greater mean PFS (24.5 months, 95% CI: 14.87-34.4) than other subtypes (P=0.005). The basal subtype had shortest mean PFS (4.37 months, 95% CI: 2.99-5.75). In overall survival (OS), luminal A had significantly higher mean OS (46.52 months, 95% CI: 39.27-53.76) than other subtypes (P=0.02). The basal subtype had shortest mean OS (18.91months, 95% CI: 10.07-27.75). On univariate analysis, breast cancer subtypes showed significant prognostic effect on OS. Hazard ratio for comparison with basal subtypes were 0.12 (95% CI, 0.03 to 0.55) for luminal A, 0.35 (95% CI, 0.08 to 1.49) for luminal B, and 0.45 (95% CI, 0.13 to 1.54) for HER-2 (P = 0.01).
CONCLUSIONS: This study suggests that the breast cancer subtypes, as approximated by hormonal receptor and HER-2 status, have significant prognostic effect on both progression free survival and overall survival. The basal and HER-2 groups had worse prognosis than luminal A and B subtypes. Luminal A has the most favorable survival than other subtypes.