

Expression of DNA repair and replication genes in non-small cell lung cancer (NSCLC): a role for thymidylate synthetase (TYMS).

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Source

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Abstract

ABSTRACT:

BACKGROUND:

BRCA1 (B), ERCC1 (E), RRM1 (R) and TYMS (T) mRNA expression has been extensively studied with respect to NSCLC patient outcome upon various chemotherapy agents. However, these markers have not been introduced into clinical practice yet. One of the reasons seems to be lack of a standard approach for the classification of the reported high/low mRNA expression. The aim of this study was to determine the prognostic/predictive impact of B, E, R, T in routinely-treated NSCLC patients by taking into account the expression of these genes in the normal lung parenchyma.

METHODS:

B, E, R, T mRNA expression was examined in 276 NSCLC samples (real-time PCR). The normal range of B, E, R, T transcript levels was first determined in matched tumor - normal pairs and then applied to the entire tumor series. Four main chemotherapy categories were examined: taxanes-without-platinum (Tax); platinum-without-taxanes (Plat); taxanes/platinum doublets (Tax/Plat); and, all-other combinations.

RESULTS:

In comparison to remotely located normal lung parenchyma, B, E, R, T mRNA expression was generally increased in matched tumors, as well as in the entire tumor series. Therefore, tumors were classified as expressing normal or aberrant B, E, R, T mRNA. In general, no marker was associated with overall and progression free survival (OS, PFS). Upon multivariate analysis, aberrant intratumoral TYMS predicted for shorter PFS than normal TYMS in 1st line chemo-naïve treated patients ($p = 0.012$). In the same setting, specific interactions were observed for aberrant TYMS with Plat and Tax/Plat ($p = 0.003$ and $p = 0.006$, respectively). Corresponding patients had longer PFS in comparison to those treated with Tax (Plat: HR = 0.234, 95% CI:0.108-0.506, Wald's $p < 0.0001$; Tax/Plat: HR = 0.242, 95% CI:0.131-0.447, Wald's $p < 0.0001$). Similar results were obtained for PFS in 1st line chemo-naïve and (neo)adjuvant pre-treated patients. Adenocarcinoma, early disease stage, and treatment with Tax/Plat doublets independently predicted for prolonged OS in patients who received only one line of treatment (adjuvant or 1st line).

CONCLUSION:

Classifying intratumoral B, E, R, T mRNA expression in comparison to normal lung may facilitate standardization of these parameters for prospective studies. With this approach, NSCLC patients with aberrant intratumoral TYMS expression will probably fare better with platinum-based

treatments.