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Blood-based Genomic Assessment of Clinical Efficacy and Toxicity of ^{177}Lu-DOTATATE of Neuroendocrine Tumors

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BACKGROUND: ^{177}Lu-DOTATATE is effective in NETs. Accurate monitoring of tumor response is constrained by radiation response. There are no effective predictors for response or toxicity. We utilized three independent blood-based gene expression assays: a 51-marker gene NETest to monitor therapeutic efficacy, PRRT Predictor Quotient (PPQ) - a molecular marker used to predict PRRT-responsiveness and a 16 gene radiation-toxicity (RAD-TOX assay) to assess hematological toxicity.

METHODS: MSKCC ^{177}Lu-DOTATATE-treated SSTR-positive GEP and lung NETs: n=55; median age 62; 47% female; 47% pancreatic; 39 G1/G2, 9 G3. All were metastatic (89% liver) and received 1-5 prior treatments (median 3) including somatostatin analogues (85%), surgery (49%), chemotherapy (53%). Response: OS and PFS. RECIST1.1; Responders: stable & partial response (DCR); Non-responders: progression. Blood collection: before each cycle and at follow-up. Samples de-identified, assay and analyses blinded. Gene expression assays: RNA isolation, real-time qPCR and multi-algorithm analyses. NETest (0-100 score). RAD-TOX score (-20 to +20). PPQ (positive = predict “responder”/negative = predict “non-responder”) at baseline. RADTOX-gene signature derived from genome-wide transcriptomic evaluations of radiation-toxicity/-sensitivity/-response gene expression studies (n=10,000 samples). Statistics: Mann-Whitney U-Test (2-tailed), Kaplan-Meier (PFS/OS), AUC.

RESULTS: 38 patients (70%) were responders. PPQ was accurate in 97% (32/33 responders). In responders, NETest decreased significantly (p=0.05) before cycle 3 (-17±9%); in "non-responders," NETest increased (+64±15%, p=0.0003).

Hematological toxicity (>Grade 2) developed in 24 (44%). RAD-TOX significantly increased (pre-PRRT: -1.94±6.8 vs. 4.7±2.7, p<0.0001) in those who developed toxicity but was unchanged in the non-toxic group (-7.6±3.6 vs. -7.9±3.7, p=0.81). AUC of RAD-TOX for predicting hematological toxicity: 0.75±0.06 (p=0.0004).

CONCLUSION: NETest decreased during ^{177}Lu-DOTATATE in responders, increased in non-responders and can be used as an early monitor of response. PPQ predicted response in 97%. RAD-TOX correlated with hematological toxicity and pre-PRRT scores predicted toxicity with 75% accuracy. Blood-based gene signatures are promising noninvasive tools to enhance management during ^{177}Lu-DOTATATE.

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