Association of plasma tumor tissue modified viral HPV DNA (TTMV) with tumor burden, treatment type, and outcome: A translational analysis from NRG-HN002.

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Background:

NRG-HN002 was a phase II trial that randomized patients with p16-positive oropharynx cancer to 60 Gy IMRT with concurrent cisplatin (IMRT-C) or 60 Gy accelerated IMRT. The protocol specified plasma collection at pretreatment (t0), intratreatment (20-28 Gy, t1), and 2 weeks to 1 month posttreatment (t2); at these timepoints, TTMV was assayed. A prespecified analysis evaluated: association of t0 TTMV to gross tumor volume (GTV) of primary and lymph nodes; t0-t1 decrease in TTMV; and association of t2 TTMV to treatment and outcome.

Methods:

TTMV was quantified as fragments/mL of plasma. If TTMV-HPV16 was not detected (<5 fragments/mL) or was a low value, the specimen was tested for TTMV-HPV18, -HPV31, -HPV33, and -HPV35. The distribution of t0 TTMV fragments was highly skewed, so these data were log-transformed; their correlation to GTV was measured by Pearson coefficient. Paired and two-sample t-tests were used to compare t0 and t1 log-transformed fragments within and between arms. Proportions of TTMV detection at t2 between arms were compared using Fisher's exact test. Rates of undetectability and fragment clearance (≥94% reduction from t0) at t2 were estimated. The negative predictive value (NPV) was estimated for 2-year locoregional failure (LRF) and progression-free survival (PFS).

Results:

Of 306 eligible patients, 164 (53.6%) donated at least one specimen. The median collection time/RT dose was -2.6 days before RT (Q1-Q3, -4.0-0.0), at 24 Gy (22-28), and 25.5 days after RT end (18-31). The t0, t1, and t2 patient participation rates were 53.6%, 45.4%, and 42.5%. Zero TTMV fragments were detected in 10.4% at t0, 19.4% at t1, and 93.1% at t2. At t0, t1, and t2, 83.5%, 79.1%, and 6.2% had detectable TTMV; 78.0%, 73.4%, and 5.4% had TTMV-HPV16. In correlating GTV to t0 TTMV fragments, the Pearson coefficient was 0.30 (95% CI 0.15-0.44). In a linear model, T stage (p=0.01) and N stage (p=0.004) were positively associated with t0 TTMV fragments. On the IMRT-C arm, the t0-to-t1 mean change was -1.06 (p=0.0009), and for IMRT, it was -0.22 (p=0.35) (p=0.03 between arms). The t2 TTMV detectability rate was 3.3% for IMRT-C vs 8.7% for IMRT (p=0.28). The t2 TTMV undetectability rate was 93.8% and the fragment clearance rate was 95.4%. Two-year LRF and PFS were 6.2% and 91.4%. The NPV of t2 undetectability was 95.0% (95% CI 89.4-98.1) for 2-year LRF and 93.3% (95% CI 87.3-97.1) for 2-year PFS, and for fragment clearance was 94.3% and 92.7%.

Conclusions:

Feasibility of the TTMV-HPV assay in clinical trial specimens was established. About 10% of p16-positive patients had zero TTMV fragments at baseline. Among those with TTMV detectability, 6.6% had types other than TTMV-HPV16. T and N stage were positively associated with TTMV fragments. The IMRT-C arm achieved rapid TTMV undetectability unlike IMRT. The NPV of posttreatment undetectability was 93-95% for 2-year LRF and PFS.