RE: Meta-analysis of the Relationship Between Dose and Benefit in Phase I Targeted Agent Trials

Recently, Gupta et al. retrospectively evaluated phase I studies of molecularly targeted agents sponsored by the National Cancer Institute’s Cancer Therapy Evaluation Program (NCI-CTEP) (1). They observed a trend for increased response rate (≥61% maximum tolerated dose [MTD] vs ≤60% MTD; odds ratio [OR] = 1.56; P = .10) and statistically significantly improved overall survival (≥61% MTD vs <20% MTD; hazard ratio = 0.37; P = .008) with higher doses. They state their findings contradict results published by our group at MD Anderson Cancer Center (MDACC) that showed low doses (≤25% MTD) yielded similar outcomes to medium (25% to <75% MTD) and high doses (≥75% MTD) (2). Gupta et al. postulate 3 reasons for diverging observations: 1) NCI-CTEP and MDACC trials were multi- vs single-institutional, respectively; 2) sample sizes were different; and 3) study periods were different.

One important distinction between the two studies is the difference in efficacy endpoints. Our study compared disease control rate, which includes patients with prolonged stable disease, and time to treatment failure (TTF), which includes patients off-stable disease, and time to treatment failure findings and findings that 2% to 5% of patients receiving low doses vs 10% to 15% of patients receiving high doses discontinued study for toxicity (P ≤ .01) (2). Furthermore, in addition to traditional response criteria, sustained stable disease can also be a meaningful efficacy measure. In view of the above, results of these studies may not be as contradictory as Gupta et al. suggest. Although the studies have differences in patient populations, institutions, sponsors, and outcome measures, our study clearly demonstrated that lower doses did not yield worse outcomes than higher doses (2). Ultimately, the impact of dose on outcome in phase I trials may depend on complex biologic, patient, and contextual factors.

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References

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