The balance between benefits and harms of molecular targeted agents

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Abstract Text:

Background: Molecular-targeted agents (MTAs) are approved by the United States Food and Drug Administration (FDA) based on improved efficacy as compared to prior standard therapy in randomized controlled trials (RCTs) but their toxicity draws less attention. Dose of MTAs and combination regimens tested in RCTs are often not justified in early phase clinical trials. Here, we compare serious toxicity of approved MTAs with control groups in pivotal RCTs and their relation to study endpoints. **Methods:** We included RCTs leading to FDA approval of MTAs from January 2000 to December 2010. Odds ratios (OR) and 95% confidence intervals were computed for treatment related toxic death and toxicity related treatment discontinuation. We also assessed the correlation between hazard ratios (HR) for overall survival (OS) and progression free survival (PFS) with OR for toxic death and for treatment discontinuation in these RCTs. **Results:** Nineteen RCTs were eligible for analysis. As compared to control groups, overall risk of toxic death significantly increased with the use of MTAs (OR=1.76, p=0.002). There was a higher rate of treatment discontinuation with MTAs compared to control groups (OR =1.62, p= 0.002). Pooled HRs for progression-free (PFS) and overall survival (OS) were 0.56 (0.50-0.62, p<0.001) and 0.78 (0.74-0.82, p<0.001) respectively (R^2=0.14). OS showed weak linear correlation with low rates of toxic death (R^2 = 0.06) and no correlation with treatment discontinuation (R^2 = 0.02); PFS showed moderate linear correlation with low rates of toxic death (R^2 = 0.3) and weak correlation with low rates of treatment discontinuation (R^2 = 0.05). **Conclusions:** New MTAs that lead to improvements in survival endpoints also significantly increase morbidity and mortality related to toxicity. Patients in RCTs are selected as having good performance status and low co-morbidity; less selected patients treated after approval of MTAs are likely to have greater probability of toxicity and lower probability of benefit than observed in the RCTs. Use of MTAs in oncologic practice should be selective and based on co-morbidity in individual patients. RCTs testing new agents should explore biomarkers associated with toxicity in addition to those associated with efficacy