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Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16.

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Abstract

BACKGROUND: The identification of surrogate endpoints that can replace true outcome endpoints is crucial to the rapid evaluation of new cancer drugs. Retrospective analyses of phase II and III trials in metastatic androgen-independent prostate cancer have shown associations between declines in serum prostate-specific antigen (PSA) levels and survival. We evaluated PSA changes as potential surrogate markers for survival by using data from a clinical trial.

METHODS: Men with androgen-independent prostate cancer were randomly assigned to either docetaxel/estramustine (D/E) or mitoxantrone/prednisone (M/P) treatment on Southwest Oncology Group Protocol 99-16. Of 674 eligible patients, 551 had a baseline PSA measurement and at least one PSA measurement during the first 3 months on protocol. PSA level declines of 5%-90% and PSA velocity at 1, 2, and 3 months were tested for surrogacy by using three statistical criteria: Prentice's criteria, the proportion of treatment effect explained, and the proportion of variation explained. All statistical tests were two-sided.

RESULTS: Three-month PSA level declines of 20%-40%, a 2-month PSA decline of 30%, and PSA velocity at 2 and 3 months met all three surrogacy criteria. For example, a 3-month PSA decline of at least 30% was associated with a more than 50% decrease in the risk of death compared with the lack of such a decline (hazard ratio [HR] = 0.43, 95% confidence interval [CI] = 0.34 to 0.55; $P < .001$), and the increased risk of death for men treated with M/P compared with D/E (HR = 1.24, 95% CI = 1.02 to 1.51; $P = .032$) lost statistical significance after adjustment for this surrogate, whereas the decrease in risk of death associated with a 3-month 30% PSA decline remained statistically significant after adjustment for treatment. PSA level declines of 50%, commonly reported in clinical trials, did not meet the criteria for surrogacy.

CONCLUSIONS: Several PSA measures satisfied the surrogacy criteria for survival in a retrospective analysis of data from SWOG 99-16. However, these measures await prospective validation in future clinical trials of chemotherapy in men with androgen-independent prostate cancer.

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Surrogate endpoints: wishful thinking or reality? [J Natl Cancer Inst. 2006]

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