Preparation and application of autologous immunohybridoma cells for the treatment of prostate cancer

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BACKGROUND Chemotherapy and second-generation androgen-targeting therapies of castration-resistant prostate cancer (CRPC) exhibit significant side effects while slightly prolonging life expectancy. In CRPC tumor cells escape immune control; hence treatments that augment the immune system have great potential. An autologous hybridoma cell (aHyC) vaccine was prepared to treat patients with CRPC in a randomized clinical trial.

METHODS

DESIGN A randomized double-blind placebo-controlled cross-over trial was conducted between June 2013 and November 2016 and followed up for survival until January 2019.

SETTING The single-institution (University Medical Centre Ljubljana, Department of Urology, Slovenia) trial was conducted in an outpatient facility.

PARTICIPANTS Based on inclusion and exclusion criteria, 22 (of 132 eligible) men with CRPC were enrolled in the trial; all were chemotherapy naive, asymptomatic, or minimally symptomatic, and were consecutively allocated to aHyC-first (12 patients) and placebo-first (10 patients) group according to previous randomization. Two patients in placebo arm were excluded, twenty were followed from diagnosis of CRPC until the trial cut-off date or death.

INTERVENTION Monocyte-derived dendritic cells (DCs) and lethally irradiated prostate tumor cells were electrofused to yield hybridomas and differentiated to the mature DC phenotype. The cell suspension was injected subcutaneously 4 times at 3-week intervals.

MAIN OUTCOMES AND MEASURES The *primary endpoints* were to assess the safety in all patients who received aHyC by recording adverse events and to assess feasibility and quality of life; the *secondary endpoints* were patients' clinical and immune responses and overall survival.

RESULTS The aHyC treatment proved safe with **no serious** adverse events (AEs), mild AEs were observed in five patients in the aHyC arm (42%) and in three patients in the placebo arm (38%; p=0.78). The aHyC treatment preserved quality of life. In the treated arm, a subpopulation of natural killer cells changed differentially in the aHyC arm: it increased by 49% less than in the placebo arm (*P*=0.04). Compared with documented controls, application of aHyC prolonged survival, remaining above the median value (13 of 19; 68%), with a 50% reduction in the relative risk of death (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.23 to 1.09), and post-hoc analysis of the time-to-next-treatment (TTNT) revealed that aHyC robustly prolonged TTNT by 4 fold versus controls (28.0 versus 6.5 months; HR, 0.23; 95% CI, 0.13 to 0.41) compared with documented controls.

CONCLUSIONS Treatment with aHyC is safe and effective, prolonging TTNT 4-fold for patients with CRPC and demonstrating, for the first time to our knowledge, that autologous dendritic cell-based vaccine has potential either as mono-immunotherapy or in combination with other CRPC therapies.