Randomized Phase III Trial of Radical Radiotherapy with Concurrent Carbogen and Nicotinamide in Locally-advanced Bladder Cancer

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Purpose/Objective(s): A pilot study in advanced bladder cancer of accelerated radiotherapy with concurrent carbogen and nicotinamide (RT+CN) suggested a therapeutic advantage relative to radiotherapy alone (RT). Subsequently, between 2000 and 2006, 333 patients have been recruited into a Phase-III randomized trial comparing RT+CN (n = 168) with RT (n = 165).

Methods/Methods: Patients with transitional cell carcinoma of the bladder, muscle-invasive carcinoma Stage T_2 or T_3 of any grade (87%), high-grade superficial carcinoma T_1 (10%), or prostatic invasion T_{4a} (3%), over the age of 18 years were eligible. Radiotherapy consisted of 55 Gy in 20 fractions in 4 weeks or 64 Gy in 32 fractions in 6.5 Weeks. Carbogen (2% CO_2 + 98% O_2) breathing at 15 breaths per minute^{-1} was administered 5 minutes before and during radiotherapy. A total of 40–60 mgkg^{-1} oral nicotinamide (Larkhall Laboratories, UK) was given 1.5–2 hours before each fraction. Primary endpoints were overall, disease-specific, and local relapse-free survival (OS DSS, LRFS). Secondary endpoints were bowel and rectal morbidity, scored using the Common Toxicity Criteria scales. Survival estimates were obtained using the Kaplan-Meier method and differences compared using the log–rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox's proportional hazard model.

Results: Overall compliance to radiotherapy was 98%. In the RT+CN arm, almost 70% complied with nicotinamide intake and 85% with carbogen administration. Three-year estimates for OS, DSS, and LRFS were 59% and 46% (log–rank p = 0.04), 68% and 56% (p = 0.1) and 74% and 63% (p = 0.1) for RT+CN and RT, respectively. The HR for risk of death from any cause was 0.8613 (CI, 0.7445–0.9955; p = 0.04) and 0.8683 (CI, 0.7307–1.0304; p = 0.1) for risk of death from local or metastatic disease, in favor of RT+CN. There was no difference between schedules for Grades 1 to 4 bowel (tenesmus, mucosal loss, sphincter control, stool frequency, and pain) and urinary (dysuria, urinary frequency, hematuria, incontinence, and decreased stream) but the incidence of Grade $2 stool frequency was higher for RT+CN (10% vs. 5%; p = 0.05).

Conclusions: A 13% survival advantage at 3 years was seen in patients treated with carbogen and nicotinamide. Disease-free and relapse-free survivals were higher in the experimental arm, but did not reach significance, possibly due to the study being underpowered. Morbidity was similar in both arms, indicating a therapeutic benefit with this approach.

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