Chemotherapy in advanced bladder cancer: analyses of treatment options and identification of molecular prognostic factors

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ABSTRACT

This PhD dissertation was carried out at Department of Oncology, Aarhus University Hospital, Molecular Diagnostic Laboratory, Aarhus University Hospital at Skejby and Department of Oncology, Herlev Hospital.

The dissertation was based on analyses of patients with stage IV urothelial cancer following standard chemotherapy with gemcitabine and cisplatin (GC).

The aims were to identify molecular markers for survival after chemotherapy, to evaluate two different schedules of the GC regimen in terms of survival and toxicity, and to evaluate post-chemotherapy strategies in patients with locally advanced disease.

By c-DNA microarray (Affymetrix-Genechip) analyses of tissue-samples from 30 patients, 55 genes with expression-values significantly correlated to survival were identified. By immunohistochemistry analyses in 149 patients, two of the gene products – Emmprin and Survivin – were validated as strong independent prognostic markers for survival.

A total of 212 patients received GC administered according to two different schedules, a 3-week and a 4-week schedule. No statistical differences in survival or response between the two schedules were observed, whereas toxicity was significantly lower, and compliance significantly increased in the 3-week schedule. A small subgroup of patients (n=13) had decreased renal function (GFR 50-60 ml/min) and received the cisplatin-dose split in two days. There were no differences in survival or response rates for these patients compared to patients with normal renal function.

A total of 84 patients had locally advanced disease. Overall median survival and 5-year survival rates were comparable to previously presented reports. Patients with complete response to chemotherapy were followed by close surveillance, with survival similar to patients presented in previous reports who had immediate cystectomy. In patients with partial response to chemotherapy, survival was improved if the patients achieved “no evidence of disease” following supplementary treatment, in particular by cystectomy.

The findings of the thesis should encourage further validation of Emmprin and Survivin as well as more markers from the 55-gene-set. In persepective, expression of Emmprin and Survivin may support decisions concerning treatment strategies for these patients.

The study of the 212 patients receiving GC shows outcome parameters equal to the outcome parameters reported in other studies, indicating a good quality of routine treatment. The results support the use of the 3-week schedule in daily clinical practice.

The findings in patients with locally advanced disease support a surveillance strategy in patients with complete response to chemotherapy as well as a strategy of subsequent treatment in patients with partial response, preferably by cystectomy.