BLADDER CANCER

Gemcitabine-based therapies offer no survival benefit

The advantages of two novel chemotherapy regimens for bladder carcinoma have been brought into question by the outcomes of recent clinical trials.

A single intravesical dose of gemcitabine following transurethral resection for non-muscle-invasive bladder cancer was found to offer no protection against recurrence compared to placebo, in a phase III randomized trial carried out at multiple centers across Germany and Turkey.

All patients with evidence of stage Ta or T1 papillary tumors were eligible for inclusion in the trial. Immediately after resection, patients were given either 2,000 mg of gemcitabine in 100 ml of saline ($n = 248$) or 100 ml of saline alone ($n = 248$) over 30–40 min. All patients then received continuous saline irrigation for at least 20 h.

Recurrence-free survival (defined as the time from randomization to either death or histological evidence of recurrence) was high in both groups—a median of 37.2 months for patients treated with gemcitabine and 40.2 months for placebo. In fact the low rate of recurrence was grounds for the trial to be halted early; after 2 years only 94 cases of recurrence were reported, 48 in the treatment group and 46 in the control cohort.

The reason for such low recurrence rates in patients who did not receive chemotherapy is unclear. Baseline disease characteristics were evenly distributed, with equivalent numbers of patients having high-risk, recurrent and multifocal disease in each group. "The constant saline irrigation may have contributed to the positive outcomes," suggests Hartwig Büttner, co-author of the study.

A single dose of chemotherapy after bladder tumor resection is recommended by the American Urological Association and European Association of Urology, and previous trials with doxorubicin, epirubicin and mitomycin have shown benefit. However, gemcitabine targets cells in the DNA replication phase only, and the authors suggest a treatment time of 30–40 min might have been too short. Gemcitabine could be better suited to a regimen of repeated instillation. "The scientific community must decide if further evidence is needed to support the current practice of early single-shot chemoinstillation in general," concludes Büttner.

The use of gemcitabine in a sequential chemotherapy schedule for metastatic transitional cell carcinoma has also been examined recently, by researchers in the US. The majority of patients (73%) responded well to 5–6 fortnightly cycles of doxorubicin and gemcitabine followed by 4 cycles of ifosfamide, paclitaxel and cisplatin (every 3 weeks). However, overall survival was reduced in comparison to treatment with ifosfamide, paclitaxel and cisplatin alone (median survival 16.4 versus 20.0 months). Thus, as the authors point out, it seems that "more chemotherapy is not necessarily better chemotherapy."

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Original articles Böhle, A. *et al.* Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomized, double-blind, placebo-controlled phase III multicentre trial. *Eur. Urol.* **56**, 495–503 (2009).
Milowsky, M. I. *et al.* Final results of sequential doxorubicin plus gemcitabine and ifosfamide, paclitaxel, and cisplatin chemotherapy in patients with metastatic or locally advanced transitional cell carcinoma of the urothelium. *J. Clin. Oncol.* **25**, 4062–4067 (2009).