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Bladder Cancer

Long-Term Survival after Gemcitabine and Cisplatin in Patients with Locally Advanced Transitional Cell Carcinoma of the Bladder: Focus on Supplementary Treatment Strategies

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Abstract

Objective: The objective was to evaluate response and survival, as well as efficacy of subsequent supplementary treatment and follow-up strategy in patients with locally advanced transitional cell carcinoma of the bladder following combination chemotherapy with gemcitabine and cisplatin (GC).
Methods: A total of 84 patients with locally advanced (T4b, Nx, M0 or Tx, N2–3, M0) received GC. After chemotherapy, the strategy was close surveillance in patients with complete response, and supplementary radical cystectomy or radiotherapy whenever possible in patients with partial response.
Results: A total of 25 patients (29.8%) with complete response to chemotherapy were followed by close surveillance. This group achieved a median overall survival of 47.6 mo. Another 25 patients had partial response to chemotherapy. Of these patients, 16 had supplementary treatment, with 10 achieving ''no evidence of disease'' (NED). Thus, a total of 35 patients achieved NED with a median overall survival of 48.7 mo versus 10.2 mo in patients not achieving NED (hazard ratio = 0.10; 95%CI, 0.05–0.20; $p < 0.0001$). The rate of NED was higher in the group of patients who had a cystectomy compared with the group who received radiotherapy as supplementary treatment.
Conclusions: In patients with locally advanced bladder cancer, NED following chemotherapy alone or chemotherapy plus supplementary cystectomy or radiotherapy is essential to achieve long-term survival. Patients with a partial response should be offered radical cystectomy whenever possible, which seems to be superior to radiotherapy. Close surveillance may be an alternative to immediate cystectomy in patients with complete response following chemotherapy.

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1. Introduction

Transitional cell carcinomas (TCCs) are the most common urothelial tumours in the Western countries, constituting approximately 95% of all cases of bladder cancer. The malignancy is among the five most common cancer types worldwide.

Approximately one of four patients will at the time of diagnosis or later present with locally advanced (T4b, N2–3) or metastatic (M1) disease [1].

These patients cannot be cured by radiotherapy or surgery alone; systemic chemotherapy is the only option. For medically fit patients, cisplatin-containing combinations are the treatment of choice.

Patients with inoperable or recurrent locoregional disease without distant metastases represent a group with a favourable prognosis, compared with patients with visceral metastases. These patients may derive a substantial benefit from cisplatin-based chemotherapy, with long-term survival rates in the range of 20–30% [2–4]. A complete response (CR) is essential for the possibility to obtain long-term remission [4] and can be achieved by chemotherapy alone or by chemotherapy followed by supplementary radical surgery or radiotherapy.

Presently, there are two standard chemotherapeutic regimens: MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or GC (gemcitabine and cisplatin) with similar survival profiles but with a significantly better toxicity profile for the GC combination [5]. Thus, GC has been widely used as a standard regimen since the year 2000.

Results after MVAC in patients with locally advanced bladder cancer have been presented by Dodd et al [6] and Herr et al [7]. In patients who obtained CR after MVAC alone or in combination with surgery, 5-yr survival rates of 30–47% were reported. Patients who were not candidates for surgery could also be offered radiotherapy [8], but data on this modality as supplementary treatment for these patients are few.

We report data on 84 patients with locally advanced TCC of the bladder who all received GC. The aim was to evaluate response and survival, as well as the outcome of our follow-up strategy in which patients with CR were offered close surveillance and patients with partial response (PR) were offered supplementary cystectomy or radiotherapy.

2. Material and methods

2.1. Patients

All patients with histologically proven, locally advanced (T4b, N2–3) TCC of the urothelium, treated with GC in a 3- or 4-wk schedule at the departments of oncology at Aarhus University Hospital and Copenhagen University Hospital in Herlev from 1 January 1997 to 1 June 2004, were included in the study. Patients were required to have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) $\leq$2, adequate bone marrow reserve (white blood cell count $\geq 3.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, and haemoglobin $\geq$10 g/dl), adequate renal function (^{51}Cr-EDTA plasma clearance $\geq$60 ml/min), and patients must have no signs of central nervous system metastases.

Patients recruited for ongoing protocols (11 patients) fulfilled all protocol criteria [5] and gave informed consent. The scientific ethics committee of Aarhus County approved all protocols.

Pretreatment evaluation consisted of physical examination, determination of ECOG-PS status, complete blood cell count, and analysis of p-alkaline phosphatase. Chest x-ray and computed tomography (CT) scans of the abdominal cavity were baseline evaluation methods; supplementary radiologic evaluation was done if other localizations of metastases were suspected. In patients with T4b tumours, lymph nodes could not always be reliably assessed and were therefore most often classified as Nx.

2.2. Treatment schedule

In the 4-wk schedule, patients received gemcitabine 1000 mg/m^2 on days 1, 8, and 15 plus cisplatin 70 mg/m^2 on day 2. Cycles were repeated every 28 d.

In the 3-wk schedule, patients received gemcitabine 1000 mg/m^2 on days 1 and 8 plus cisplatin 70 mg/m^2 on day 2. Cycles were repeated every 21 d.

Gemcitabine and cisplatin were administered intravenously over 30–60 min. Cisplatin was administered with adequate pre- and posthydration. Supportive care, including antiemetics, analgesics, blood transfusions, and antibiotics, was administered as appropriate. Granulocyte colony-stimulating factors were not used routinely.

The choice of either the 3-wk or 4-wk schedule was based on actual protocols for that specific time period, not on selected patient parameters. Thus, during the specific time periods, all patients had the same schedule, including patients treated outside the framework of a protocol.

2.3. Evaluation of patients

Response was classified according to World Health Organization criteria [9].

Evaluation of response was performed radiologically by the same methods as the baseline assessment. Response was reassessed every two cycles. Cystoscopy was performed after the last treatment cycle. A negative cystoscopy including negative biopsies was a prerequisite for classification as CR. A patient with a radiologic CR but with residual tumour cells at the subsequent cystectomy was classified as PR.

No evidence of disease (NED) after supplementary treatment was defined as complete removal of disease by the surgeon, in case of cystectomy, or a negative cystoscopy including negative biopsies, in case of radiotherapy.

Progression-free and overall survivals were measured from the day of start of chemotherapy until the day of progression