Carboplatin Based Induction Chemotherapy for Nonorgan Confined Bladder Cancer—A Reasonable Alternative for Cisplatin Unfit Patients?

Laura S. Mertens, Richard P. Meijer, J. Martijn Kerst, Andries M. Bergman, Harm van Tinteren, Bas W. G. van Rhijn and Simon Horenblas*

From the Departments of Urology (LSM, RPM, BWGvR, SH), Medical Oncology (JMK, AMB) and Medical Statistics (HvT), The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Abbreviations and Acronyms

CBCC = cisplatin based combination chemotherapy

cCR = clinical complete response

CT = computerized tomography

DSS = disease specific survival

gem/carbo = gemcitabine and carboplatin

gem/cis = gemcitabine and cisplatin

LN = lymph node

MVAC = methotrexate, vinblastine, doxorubicin and cisplatin

OS = overall survival

pCR = pathological complete response

RC = radical cystectomy

RFS = recurrence-free survival

UC = urothelial carcinoma

Submitted for publication February 2, 2012.

* Correspondence: Department of Urology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands (telephone: +31-20-5122553; FAX: +31-20-5122554; e-mail: s.horenblas@nki.nl).

For another article on a related topic see page 1346.

Purpose: We investigated induction carboplatin based chemotherapy in patients with nonorgan confined urothelial carcinoma who were considered unfit for cisplatin. A comparison was made with patients who received induction cisplatin based combination chemotherapy.

Materials and Methods: We identified 167 patients with nonorgan confined urothelial carcinoma who received induction cisplatin based combination chemotherapy (126) or gemcitabine and carboplatin (41) at our hospital between 1990 and 2010. Of the patients 124 completed 4 cycles of cisplatin based combination chemotherapy or gemcitabine and carboplatin. Clinical response (ycTNM) was evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. Radical cystectomy and bilateral extended pelvic lymph node dissection were performed in 106 patients. A pathological complete response was defined as no evidence of disease (ypT0N0). Disease specific survival was analyzed using the Kaplan-Meier method. Multivariate analysis was performed.

Results: Complete clinical response rates did not differ significantly among the treatment groups. A pathological complete response was seen in 33.7% of specimens in the cisplatin based combination chemotherapy group vs 30.3% in the gemcitabine and carboplatin group ($p = 0.808$). We found no significant difference in disease specific survival between patients who started cisplatin based combination chemotherapy and those who started gemcitabine and carboplatin. For patients who completed 4 cycles and underwent radical cystectomy there was also no significant difference in disease specific survival between the groups. On multivariate analysis a pathological complete response was the only variable significantly associated with disease specific survival ($p < 0.045$).

Conclusions: Induction gemcitabine and carboplatin for nonorgan confined urothelial carcinoma achieves clinical and pathological response rates, and survival outcomes comparable to those of the cisplatin based combination chemotherapy schemes. Our data suggest that a carboplatin based regimen can be considered a reasonable alternative for cisplatin unfit patients in the preoperative setting.

Key Words: urinary bladder, urinary bladder neoplasms, urothelium, carboplatin, cisplatin

INDUCTION cisplatin based chemotherapy demonstrated a 6% absolute survival benefit for muscle invasive bladder cancer.[1–5] The treatment of choice is CBCC. However, safe administration of CBCC is not always possible.[6,7]

0022-5347/12/1884-1108/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2012.06.018
Vol. 188, 1108-1114, October 2012
Printed in U.S.A.

A major disadvantage of CBCC is its severe cumulative renal toxicity. Since UC is largely a disease of elderly individuals with age, lifestyle and disease associated decreased renal function and performance status, a high rate of severe acute toxicity and impaired renal function is a major threat of CBCC treatment.

Recently a consensus was formulated to define patients with metastatic UC who are unfit for CBCC. CBCC treatment is considered not feasible in patients who meet at least one of several criteria, including 1) WHO or ECOG (Eastern Cooperative Oncology Group) performance status 2 or higher, or Karnofsky performance status 60% to 70% or lower, 2) calculated or measured creatinine clearance less than 60 ml per minute, 3) CTCAE (Common Terminology Criteria for Adverse Events) version 4, grade 2 or above audiometric hearing loss, 4) CTCAE version 4, grade 2 or above peripheral neuropathy and/or 5) NYHA (New York Heart Association) class III or greater heart failure.[6] According to these criteria approximately 30% to 50% of patients with locally advanced and/or LN positive UC are considered unfit for cisplatin.[8]

The toxicity of the regimen and the greater age of many patients may impair the widespread use of induction CBCC. As an alternative, carboplatin based regimens may be considered. Currently to our knowledge no data support carboplatin based regimens as the second best regimen in patients with UC treated in the preoperative setting. Thus, we investigated the potential benefit of carboplatin based regimens in patients with nonorgan confined UC who were considered unfit for induction cisplatin treatment and compared this with patients who received a first choice CBCC induction regimen.

MATERIALS AND METHODS

Patients

From our institutional bladder cancer database we identified 167 consecutive patients with nonorgan confined UC of the bladder who presented at our hospital and received induction chemotherapy between 1990 and 2010. All patients had locally advanced bladder UC, ie stage cT3-4a, and/or regional (N+) and/or supraregional (para-aortal/paracaval) nodal involvement (nodal involvement below the renal vein) (M+). Study exclusion criteria were bladder tumors other than UC, previous chemotherapy and evidence of distant metastasis.

Pretreatment Staging

Patients were staged by physical examination, cystoscopy, laboratory studies and imaging (at least abdominopelvic CT and chest x-ray). Renal function (glomerular filtration rate) was calculated according to the modified diet in renal disease formula. Radiological evidence of LN metastasis was considered in cases of pathologically enlarged LN greater than 1 cm in diameter or strong suspicion on positron emission tomography/CT. In 82% of these cases suspicious LN lesions were proved by histology (biopsy or dissection) or cytology (fine needle aspiration). In general, suspect LNs were not biopsied if other criteria for induction chemotherapy were present. Preoperative tumor stage was determined according to the UICC.[9]

Induction Chemotherapy

At our hospital patients with cT3-T4a and/or N+/M+ disease (supraregional or regional nodal metastases but below the renal vein) are considered candidates for induction chemotherapy. The recommendation for induction chemotherapy was made after multidisciplinary consultation (medical oncology, urology, pathology, radiology and radiation oncology). CBCC or carboplatin based combination therapy was advised. CBCC consisted of an accelerated or classic MVAC regimen, as described by Nieuwenhuijzen et al,[10] or gem/cis (gemcitabine 1,000 mg/m^2 and cisplatin 70 mg/m^2 on day 1, and gemcitabine 1,000 mg/m^2 on day 8) in a 21-day cycle. At our hospital accelerated MVAC is the preferred cisplatin based regimen. Patients considered unfit for CBCC were selected to receive gem/carbo. Selection criteria corresponded to those described by Galsky et al, including impaired renal function, comorbidities and low performance status.[6] Starting dose levels were AUC 5 carboplatin on day 1 (30 minutes) and 1,000 to 1,250 mg/m^2 gemcitabine for 30 minutes on days 1 and 8 for a 21-day cycle.

Response Evaluation

Response was assessed after 2 and 4 cycles with cystoscopy, restaging CT and/or positron emission tomography/CT. Clinical post-chemotherapy status (ycTNM) was evaluated according to RECIST 1.1.[11] When there was clinically progressive disease after 2 courses, chemotherapy ceased and the patient was evaluated for further therapy, ie surgery, radiotherapy or palliation only. We compared clinical response rates between the treatment groups for patients who completed 4 cycles of the regimen. Patients who did not complete 4 chemotherapy cycles or who switched from 1 chemotherapeutic regimen to another were analyzed as a separate group.

Histopathology

The decision to perform subsequent surgery (extended pelvic LN dissection and RC) was made after a second multidisciplinary discussion. Histopathological investigation of pathology specimens was used as the gold standard for response evaluation. pCR was defined as no evidence of tumor in the bladder and lymphatic tissue (ypT0N0) and a partial response was defined as any down-staging from baseline. Although surgery was uniformly advised in responding patients, some refused and went on to receive preferred curative radiotherapy or followup. We compared pathological response rates between the 2 treatment groups for patients who completed 4 cycles of the regimen and underwent RC and extraperitoneal LN dissection.

Statistics

Differences in patient characteristics and response rates were evaluated using the Pearson chi-square and Fisher exact tests. RFS, DSS and OS were analyzed using the Kaplan-Meier method. OS was defined as the time from