Novel Bladder Preservation Therapy with Osaka Medical College Regimen

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Purpose: We investigated the effect of balloon occluded arterial infusion of an anticancer agent (cisplatin/gemcitabine), used concomitantly with hemodialysis, which delivers an extremely high concentration of anticancer agent to the tumor site without systemic adverse effects, along with concurrent radiation (referred to as the Osaka Medical College regimen) in patients with advanced bladder cancer.

Materials and Methods: A total of 329 patients (TisN0 16, T2N0 174, T3N0 77, T4N0 22 and TxN+ 40) were assigned to receive the Osaka Medical College regimen. Patients who did not achieve complete response underwent total cystectomy or secondary balloon occluded arterial infusion with an increased amount of cisplatin and/or gemcitabine.

Results: The Osaka Medical College regimen allowed 83.6% (276 of 329) of patients in total and 93.6% (250 of 267) of patients with organ confined disease (including T3b) to achieve complete response. Of the patients with a complete response 96% (240 of 250) survived with a functional bladder without evidence of recurrent disease within a mean followup of 159 weeks. Although lymph node involvement, especially N2 stage, was selected as a significant risk factor for treatment failure and survival, it was noteworthy that 61.9% of patients with N1 disease achieved complete response and that the 5-year overall survival rate was 72.2%. No patients had grade III or more severe toxicities.

Conclusions: The Osaka Medical College regimen, a new bladder preservation strategy, can be curative not only in patients for whom cystectomy is indicated, but also in patients whose condition is not amenable to curative treatment because of disease stage, age or other factors, and for whom merely palliative therapy would otherwise seem the only option.

Key Words: balloon occlusion; infusions, intra-arterial; hemodialysis solutions; urinary bladder neoplasms

Abbreviations and Acronyms

BOAI = balloon occluded arterial infusion
CR = complete response
HD = hemodialysis
LN = lymph node
OMC = Osaka Medical College
UC = urothelial carcinoma

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TRIMODALITY therapy involving radical transurethral resection, chemotherapy and radiation therapy has long been attempted as an alternative approach for patients who require cystectomy. The Radiation Therapy Oncology Group completed 6 prospective protocols entering 415 patients with T2-T4a muscle invasive bladder cancer who were candidates

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for cystectomy. However, none of the protocols achieved a 5-year survival rate of more than 60%.[1,2] Improvement of the survival rate may require a new method which allows delivery of a higher dose of anticancer agent specifically into the bladder, without causing systemic side effects. Therefore, we developed a novel bladder preservation therapy, the OMC regimen, involving balloon occluded arterial infusion of an anticancer agent and concurrent hemodialysis, which allows the anticancer agent to accumulate at a high concentration in the bladder as well as the surrounding tissues, while ensuring that the systemic concentration remains low after the agent has passed through the tumor, followed by radiation therapy. We performed the OMC regimen as neoadjuvant chemoradiotherapy followed by radical cystectomy, and found no cancer in the pathological specimens from any of the patients (3). We then started to apply this treatment as a primary therapy. We describe the details of this approach and the outcomes to date.

MATERIALS AND METHODS

Eligibility Criteria

Eligible patients had histologically confirmed carcinoma in situ, or stage T2, T3 or T4 muscle invasive bladder cancer without distant metastasis. Patients with pelvic LN metastasis were also eligible for study inclusion.[3,4] All patients who received the OMC regimen had an absolute neutrophil count of 1,500/μl, platelets 100,000/μl, creatinine 3.0, bilirubin 3 times the institutional upper limit of the normal range, aspartate aminotransferase 4 times the institutional upper limit of the normal range and ECOG (Eastern Cooperative Oncology Group) performance status 0-2. The study was reviewed and approved by the Osaka Medical College institutional review board. Patients were informed of the investigational nature of the study and provided written informed consent before study enrollment.

Treatment Details

Patients received the OMC regimen 4 to 5 weeks after transurethral resection of their bladder tumors. For intra-arterial infusion we used an intra-arterial catheter equipped with 2 occlusion balloons.[3,4] Figure 1 illustrates the extracorporeal circuit used for treatment. We administered 100, 200 or 300 mg cisplatin as a single bolus through the catheter during a 1-hour period, according to the criteria described in table 1 and our previous report.[3,4] Hemodialysis was performed simultaneously via a double lumen catheter placed in the vena cava for 2 hours after the start of arterial infusion.

Radiation therapy was administered to the whole pelvis using a computerized tomography planned 3-dimensional conformal technique to a total of 60 Gy, as 50 Gy (2 Gy per day × 25 days) followed by 10 Gy (2 Gy per day × 5 days) of local irradiation to the bladder. The planned target volume for the bladder included the gross target volume (empty bladder plus any extravesical tumor) with a 1 cm expansion. The response was evaluated by transurethral resection at 6 weeks (and not earlier, to allow distinction between viable residual cancer cells and those undergoing degeneration due to the effects of treatment).

Assessment, Toxicity and Response Criteria

During treatment the toxicity was monitored weekly using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Patients who achieved CR were observed using our followup protocol. Any evidence of residual tumor in the bladder was deemed treatment failure. Such patients were primarily advised to undergo total cystectomy when possible, or secondary BOAI with a higher dose of cisplatin or gemcitabine (1,600 mg) as salvage therapy. Patients with only a superficial amount of remaining tumor received intravesical injection of bacillus Calmette-Guérin.

Statistics

Simple and multiple logistic regression analyses were conducted to evaluate the significance of several variables as risk factors for treatment failure including age, gender, tumor stage, tumor size, hydronephrosis, LN status and histology. Life table probabilities of overall survival and progression-free survival were determined using Kaplan-Meier analysis and the log rank test. Cox proportional hazards analysis was conducted to assess the interassociations of these factors. Differences at $p < 0.05$ were considered statistically significant.

RESULTS

Patient Characteristics

Between 1988 and 2014, 329 patients were treated with the OMC regimen. Mean patient age was 68 years (range 30 to 98). The characteristics of the patients are shown in table 2.

Response to OMC Regimen

Supplementary table 1 (http://jurology.com/) summarizes the treatment response. In total 83.6% of patients achieved CR. The overall response rate was 93.9% (complete response 83.6%, partial response 6.38%, stable disease 3.95%) and 86.4% of those patients survived without recurrence after a mean followup of 133 weeks. Of the patients who did not achieve CR after primary therapy with the OMC regimen (54 of 329, 16.4%) only 3 underwent total cystectomy while 18 received BOAI with gemcitabine as salvage therapy (CR 22%) and some were on the waiting list.

Logistic regression analyses revealed that LN involvement, T4 stage, tumor histology (nonUC) and hydronephrosis were significant risk factors for treatment failure (supplementary table 2, http://jurology.com/). In fact, 93.6% (250 of 267) of patients with organ confined disease (including T3b) achieved CR and 96% (240 of 250) of those patients survived with a functional bladder without recurrence or distant metastasis within a mean followup