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Original article

Significance of preoperative butyrylcholinesterase as an independent predictor of survival in patients with muscle-invasive bladder cancer treated with radical cystectomy

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Abstract

Objectives: Butyrylcholinesterase (BChE) is an alpha-glycoprotein found in the nervous system and liver. Its serum level is reduced in many clinical conditions, such as liver damage, inflammation, injury, infection, malnutrition, and malignant disease. In this study, we analyzed the potential prognostic significance of preoperative BChE levels in patients with muscle-invasive bladder cancer (MIBC) undergoing radical cystectomy (RC).

Methods and materials: We retrospectively evaluated 327 patients with MIBC who underwent RC from 1996 to 2013 at a single institution. Serum BChE level was routinely measured before operation in all patients. Covariates included age, gender, preoperative laboratory data (anemia, BChE, lactate dehydrogenase, and C-reactive protein), clinical T (cT) and N stage (cN), tumor grade, and RC with/without neoadjuvant chemotherapy. Univariate and multivariate analyses were performed to identify clinical factors associated with overall survival (OS) and disease-free survival (DFS). Univariate analyses were performed using the Kaplan-Meier and log-rank methods, and the multivariate analysis was performed using a Cox proportional hazard model.

Results: The median BChE level was 187 U/l (normal range: 168–470 U/l). The median age of the enrolled patients was 69 years, and the median follow-up period was 51 months. The 5-year OS and DFS rates were 69.6% and 69.3%, respectively. The 5-year OS rates were 90.1% and 51.3% in the BChE $\geq$168 and $<$168 U/l groups, respectively ($P < 0.001$). The 5-year DFS rates were 83.5% and 55.4% in the BChE $\geq$168 and $\leq$167 U/l groups, respectively ($P < 0.001$). In the univariate analysis, BChE, cT, cN, and RC with/without neoadjuvant chemotherapy were significantly associated with both OS and DFS. Multivariate analysis revealed that BChE was the factor most significantly associated with OS, and BChE, cT, and cN were significantly associated with DFS.

Conclusions: This study validated preoperative serum BChE levels as an independent prognostic factor for MIBC after RC.

Keywords: Butyrylcholinesterase; Muscle-invasive bladder cancer; Biomarker; Overall survival; Disease-free survival

1. Introduction

Radical cystectomy (RC) remains the gold standard of treatment for patients with muscle-invasive bladder cancer (MIBC) and for those with high-risk, recurrent, noninvasive disease, as it is effective in improving local control and long-term disease-free survival (DFS) [1]. Despite local definitive therapies, such as RC, approximately 50% of patients with MIBC will develop distant metastasis and die of bladder cancer [2,3]. However, clinical courses of patients with MIBC vary and are difficult to predict preoperatively. Most studies investigating MIBC prognosis are retrospective and have evaluated postoperative prognostic parameters, such as pathological T stage and lymphovascular invasion, which are available after RC. To date,

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several studies have reported a relationship between survival and pretreatment clinical features, including C-reactive protein (CRP) level [4], neutrophil-to-lymphocyte ratio [5], and elevated platelet count [6].

Systemic inflammation is a common host reaction to carcinogenesis or cancer progression, and serum levels of butyrylcholinesterase (BChE) have been reported to reflect the presence of inflammation and other clinical conditions [7]. BChE is an alpha-glycoprotein found primarily in the central and peripheral nervous system and the liver, and in lower levels in most tissues. The serum level of BChE has been found to decrease during the course of many clinical conditions, such as liver damage, inflammation, injury, and malnutrition [8]. A decreased pretreatment serum BChE level has also been reported as a useful parameter in patients with advanced cancer with or without hepatic involvement [7,9,10]. However, the predictive value of serum BChE levels in patients with bladder cancer is unknown. Thus, we evaluated the prognostic significance of pretreatment BChE in patients with MIBC undergoing RC.

2. Methods and materials

2.1. Study population

In this retrospective study, we reviewed the clinical and pathological records of 327 patients with MIBC who underwent RC and bilateral pelvic lymphadenectomy (PLND) with or without neoadjuvant chemotherapy (NAC) between May 1996 and December 2012 at Hirosaki University. Eligible patients had histologically confirmed stage T2 to T4a muscle-invasive urothelial carcinoma of the bladder without distant metastasis. There were no restrictions concerning the NAC regimens. Patient characteristics collected for analysis included age, gender, preoperative laboratory data (anemia, BChE, lactate dehydrogenase [LDH], and CRP), clinical T (cT) and N stage (cN), tumor grade, and RC with/without NAC. Information on patients and tumor characteristics was obtained from medical charts.

The study protocol and informed consent documents were reviewed and approved by the Hirosaki University institutional review board.

2.2. Treatment

Of the 327 included patients, 162 patients received neoadjuvant gemcitabine and carboplatin (GCarbo) [11], 22 received neoadjuvant cisplatin and doxorubicin arterial infusion (BOAI), and 143 underwent RC alone. In the GCarbo group, patients received 2 cycles of 800-mg/m^2 gemcitabine, and carboplatin at an area under the curve of 4. All patients with MIBC at our institution received neoadjuvant GCarbo therapy from 2005. Conversely, the patients who were treated before 2004 or who showed cancer progression during neoadjuvant GCarbo therapy received BOAI as a second therapy. In the BOAI group, patients received 2 cycles of 70-mg/m^2 cisplatin and 30-mg/m^2 doxorubicin. Our surgical technique with regard to RC and PLND has been previously described in detail [12,13]. The choice of urinary diversion was determined according to the surgeon's discretion or the patient's preference or both. PLND, including removal of the hypogastric, external iliac, obturator, presacral, and common iliac lymph nodes up to the aortic bifurcation, was routinely performed.

2.3. Patient evaluation

The following baseline information was obtained for each patient: complete history and physical examination findings, Eastern Cooperative Oncology Group performance status, abdominal and pelvic computed tomography (CT) or magnetic resonance imaging, and chest radiography or CT.

The diagnosis of MIBC was confirmed by a single pathologist at our institution by reviewing the results of transurethral resection and the baseline magnetic resonance imaging findings.

Levels of serum BChE (normal range: 168–470 U/l), LDH (normal range: 119–229 U/l), CRP (normal range: 0–0.3 mg/dl), serum albumin (Alb) (normal range: 3.6–5.0 g/ml), and hemoglobin (Hb) (normal range: 13.5–17.0 g/dl) were measured a week before RC or NAC. A low BChE level was defined according to the area under the receiver operating characteristic curve. The cutoff point was defined as the minimal value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ [14]. None of the patients showed any evidence of active infection or inflammatory disease at the time of surgery.

Specimens obtained during cystoprostatectomy were extensively examined to determine the presence of MIBC. We performed a pathological examination of complete transmural sections of the bladder wall to accurately determine the pathological stage of the tumor. In addition, histological examination of several sections from various sites within the bladder, including the dome, anterior wall, lateral walls, posterior wall, trigone, and both the ureters, was performed to identify superficial disease or a second primary tumor.

Tumor staging was performed according to the staging system defined in the American Joint Committee on Cancer Staging Manual [15]. All lymph nodes from each designated site and representative sections of the surrounding fibroadipose tissue were examined.

2.4. Follow-up schedule

Each patient was evaluated every 3 months using ultrasonography (to check for hydronephrosis), urine cytology, and renal and liver function tests. CT for the chest to the pelvis was performed every 6 months for 5 years and annually thereafter.