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ORIGINAL ARTICLE

Possible risk of overestimation of renal function using cystatin C-based eGFR in testicular cancer survivors treated with cisplatin-based chemotherapy

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Abstract
Background Chronic kidney disease (CKD) is a major long-term morbidity of testicular cancer (TC) survivors cured by cisplatin-based chemotherapy. We conducted the present study to elucidate the usefulness of cystatin-based estimated glomerular filtration rates (eGFRcys) for diagnosis of CKD compared to creatinine-based eGFR (eGFRcreat) in those patients.
Methods eGFRcys and eGFRcreat were measured in 53 TC survivors. The 24-h creatinine clearance (CrCl) was measured in 12 TC survivors and 17 CKD patients with medical disease; all of them had eGFRcreat <60 m/min/1.73 m^2. Also, urinary beta2-microglobulin and albumin concentrations in spot urine specimens were measured.
Results The mean eGFRcreat was significantly lower than eGFRcys, at 67.9 and 95.2 ml/min/1.73 m^2, respectively ($p < 0.05$). The prevalence of stage 3–5 CKD differed by GFR estimation methods. It was 47.2% with eGFRcreat and only 7.5% with eGFRcys. There were 21 patients with eGFRcreat <60 ml/min/1.73 m^2 and eGFRcys ≥60 ml/min/1.73 m^2. In all 12 TC survivors, the eGFRcys values were higher than both eGFRcreat and GFR (24-h CrCl). In contrast, no difference was observed among eGFR values in the 17 patients with CKD due to medical disease. Ten of 21 patients with eGFRcreat <60 ml/min/1.73 m^2 and eGFRcys ≥60 ml/min/1.73 m^2 showed significant beta2-microglobulinuria: a higher prevalence than that in patients with both eGFRs ≥60 ml/min/1.73 m^2. Also, the incidence of microalbuminuria tended to be high in those patients.
Conclusions The present study suggests that eGFRcys may overestimate renal function in TC survivors cured by cisplatin-based chemotherapy.

Keywords Testicular cancer · Cisplatin · Chemotherapy · Chronic kidney disease · Estimated glomerular filtration rate · Cystatin C

Introduction

Testicular cancer (TC) is common in young men, and is one of the most curable cancers when appropriately treated by cisplatin-based chemotherapy and surgery. Given the high cure rate and life expectancy of such young patients, the assessment of long-term morbidity is very important [1, 2]. Morbidities include secondary malignant neoplasms, neuropathy, gonadal dysfunction, cardiovascular disease, and nephrotoxicity.

In TC chemotherapy, where cisplatin is the key drug, acute kidney injury (AKI) has been well described. In contrast, there has been limited data on long-term nephrotoxicity in TC survivors. Several studies demonstrated a 20–30% reduction in the glomerular filtration rate (GFR); however, most of these studies suffered from small sample sizes and relatively short-term follow-up periods [3–5]. This may be partly because GFR measurement is cumbersome. In addition, differences in the methods for GFR evaluation make it difficult to interpret the results.

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To overcome these obstacles, several investigators including ourselves have recently introduced the concept of chronic kidney disease (CKD) defined by the estimated GFR (eGFRcreat) based on serum creatinine (sCR) into management of testicular cancer survivors [6–8]. However, the reported prevalence of CKD with eGFRcreat less than 60 ml/min/1.73 m^2 ranged from 10 to 23% in the different studies. In addition to the difference in intensity of the delivered chemotherapy, several other factors including muscle mass, age and race might influence the eGFR estimation using sCR.

Cystatin C is a low-molecular-weight protein produced from all nucleated cells, and it can be filtered from glomeruli and reabsorbed from the proximal tubuli and catabolized. It is well known that age, race, gender and muscle mass have no effect on the serum cystatin C level [9]. Several studies have indicated that cystatin C is a more sensitive marker than sCR for a decrease in GFR, and could be an excellent marker for eGFR (eGFRcys) [10, 11]. In the field of oncology, some investigators have reported that serum cystatin C is superior to sCR in detecting acute renal impairment during or just after cisplatin-based chemotherapy [12, 13], whereas other authors reported contradictory results [14, 15].

In this study, we analyzed both eGFRcreat and eGFRcys of 53 metastatic TC patients treated at Tsukuba University Hospital (TUH). The present study was conducted to clarify the usefulness of eGFRcys compared to eGFRcreat for diagnosis of CKD in TC survivors after cisplatin-based chemotherapy. In the present study, we showed several interesting but unexpected results.

Table 1 Patient characteristics

Patients	53
Follow-up (months)	
Median	72
Range	12–360
Age (years) at chemotherapy	
Median	34
Range	17–54
Hydronephrosis	
Yes	5 (9)
No	48 (91)
Pathological findings	
Seminoma	6 (11)
Non-seminoma	47 (89)
IGCCCG classification	
Good	20 (38)
Intermediate	13 (24)
Poor	20 (38)
Pretreatment eGFR[a]	
Median	96.5
Range	48.7–166.2
Below 59	3 (6)
60-89	15 (28)
Above 90	31 (58)
Unknown	4 (8)
Total dosage of CDDP (mg/m^2)	
Below 400	31 (58)
Above 400	22 (42)

[a]ml/min/1.73 m^2

Materials and methods

Patients

The present study was performed as part of a prospective study of investigative research for quality of life and long-term complications in TC survivors (H24-23). Written informed consent for laboratory tests evaluating renal function in addition to a routine check-up for tumor markers was obtained from each patient. We enrolled a total of 53 metastatic TC patients who had been treated by cisplatin-based chemotherapy at TUH between 1982 and 2010. The patient characteristics are summarized in Table 1. The median age at diagnosis was 34 years (range 17–54 years). At the enrollment into the study, all patients were in continuous cancer-free status. The median follow-up period from the completion of chemotherapy was 75.9 months (13.7–337 months). The median patient age at the time of the study was 44 years (range 24–64 years).

The histology of the testicular tumors was seminoma in 6 patients and non-seminoma in 47 patients. According to the IGCCCG classification [1], 20, 13, and 20 patients were classified as having good, intermediate, and poor prognoses, respectively. The median pretreatment eGFRcreat of all patients was 96.5 (48.7–166.2) ml/min/1.73 m^2. Three patients showed pretreatment eGFRcreat below 60 ml/min/1.73 m^2 (mean 52.2 ml/min/1.73 m^2). Five patients had hydronephrosis due to retroperitoneal lymph node (RPLN) metastasis, and were treated with ureteral stent placement before the start of chemotherapy. The mean pretreatment eGFRcreat of those 5 patients was 88.2 ml/min/1.73 m^2.

Treatment for testicular cancer

All 53 patients received cisplatin-based induction chemotherapy. Of them, 42 were treated with a BEP protocol consisting of bleomycin, etoposide, and cisplatin [16]. BEP consisted of 100 mg/m^2 of etoposide and cisplatin on days 1–5, and 30 mg/body of bleomycin on days

1, 8 and 15 with recycling on day 22. Another 3 patients received the PVB regimen (cisplatin, vinblastine, and bleomycin). The remaining 7 patients received EP (etoposide and cisplatin) or VIP (etoposide, ifosfamide, and cisplatin) [16] as induction chemotherapy. In PVB, EP and VIP, treatment cycle and dose of cisplatin was same as BEP. In PVB, vinblastine 0.15 mg/kg on days 1 and 2 was administrated instead of etoposide, otherwise same as BEP. In VIP, etoposide reduced to 75 mg/m^2 and 1.2 g/m^2 of ifosfamide on days 1–5 was used instead of bleomycin. In addition to the induction chemotherapy, 24 patients received second-line or more chemotherapy. The most frequently used second-line chemotherapy regimen was TIP (paclitaxel, ifosfamide, and cisplatin) [16]. In TIP, 175 mg/m^2 of paclitaxel was administrated instead of etoposide, followed by ifosfamide and cisplatin same as VIP. Thirteen patients needed third-line or further chemotherapy. The median number of chemotherapy cycles of all patients was 4.0. Twenty-two (42%) patients received five or more of cycles of cisplatin-based chemotherapy (Table 1). Overall, 12 patients underwent retroperitoneal lymph node dissection (RPLND) after chemotherapy. One patient needed adjunctive nephrectomy at RPLND.

Laboratory tests

Serum and urinary creatinine levels were measured by an enzymatic method. The serum concentration of cystatin C was determined by a latex particle-enhanced turbidimetric immunoassay (LSI Medience Corp, http://www.medience.co.jp). Urinary beta2-microglobulin and albumin concentrations in spot urine specimens were determined by a latex particle-enhanced turbidimetric immunoassay and immunoturbidimetric method. Beta2-microglobulinuria was defined as urinary beta2-microglobulin $\geq$500 ng/ml. Microalbuminuria was defined as a urine albumin-to-creatinine ratio $\geq$30 mg/g creatinine (Cr).

Evaluation of renal function

The eGFRcreat was calculated using the formula reported by Matsuo et al. [17]. This equation originated from the Modification of Diet in Renal Disease (MDRD) study group [18], and was adjusted for Japanese individuals and recommended by the Japanese Society of Nephrology (JSN): eGFRcreat (ml/min/1.73 m^2) = 194 $\times$ sCr$^{-1.094}$ $\times$ age [years])$^{-0.287}$. The eGFRcys was calculated using the Japanese eGFRcys equation reported by Horio et al. as follows [19]: $\text{eGFRcys}\ (\text{ml}/\text{min}/1.73\text{m}^2) = (104 \times \text{Cys}^{-1.019} \times 0.996^{\text{age[years]}}) - 8$. The equation was based on serum cystatin C values measured by a colloidal gold immunoassay (Alfresa Pharma, http://www.alfresa-pharma.co.jp). Therefore, the cystatin C values measured by the latex particle-enhanced turbidimetric immunoassay were converted into estimated values of colloidal gold immunoassay using the formula proposed by a project team for verification of immunoassay standardization for serum cystatin C from the Japan Society of Clinical Chemistry [20]. In 12 TC patients, the 24-h creatinine clearance (24-h CrCl) was measured in outpatient clinic. In addition, we measured 24-h CrCl in 17 CKD patients with medical disease, including 7 kidney transplant recipients, 4 patients with nephrotic syndrome, 2 with Ig A nephropathy and 4 with miscellaneous diseases. The 24-h CrCl was calculated from urinary creatinine $\times$ urinary volume (24 h)/sCR. To allow comparison, GFR based on CrCl, GFR (24-h CrCl), was determined by multiplying the original value by 0.719, and normalized to standard values of 1.73 m^2 BSA. The body surface area (BSA) was calculated as follows: BSA (m^2 = (body weight [kg]) 0.425 $\times$ (body height [cm]) 0.725 $\times$ 0.007184 [21].

Statistical analyses

Continuous data are expressed as means $\pm$ standard errors. Wilcoxon signed rank test and Mann–Whitney's U test were used to compare the mean values. The proportion of beta2-microglobulinuria and microalbuminuria in each patient group was compared by the χ^2 test. A value of $p < 0.05$ was considered statistically significant. All of the statistical analyses were performed using the STAT View software (version 5.0, SAS Institute, Inc., Cary, NC, USA).

Results

Prevalence of stage 3–5 CKD defined by eGFRcreat and eGFRcys

The sCR values were abnormally elevated (normal range 0.61–1.04 mg/dl) in 25 (47%) of 53 patients. In contrast, only 16 patients showed abnormal serum cystatin C levels (normal range 0.63–0.95 mg/l). As shown in Fig. 1a, there was a marked difference between eGFRcreat and eGFRcys. The mean eGFRcreat was significantly lower than eGFRcys; 67.9 and 95.2 ml/min/1.73 m^2, respectively ($p < 0.05$). As a result, the prevalence of stage 3–5 CKD differed according to the method of GFR estimation. When using eGFRcreat, 23 patients were diagnosed with stage 3 CKD (30–59 ml/min/1.73 m^2). In addition, one patient each was diagnosed with stage 4 CKD (15–29 ml/min/1.73 m^2) and stage 5 CKD (<15 ml/min/1.73 m^2). When evaluated with eGFRcys, only 2 patients (3.8%) were diagnosed with stage 3 CKD. Additional 2 patients were

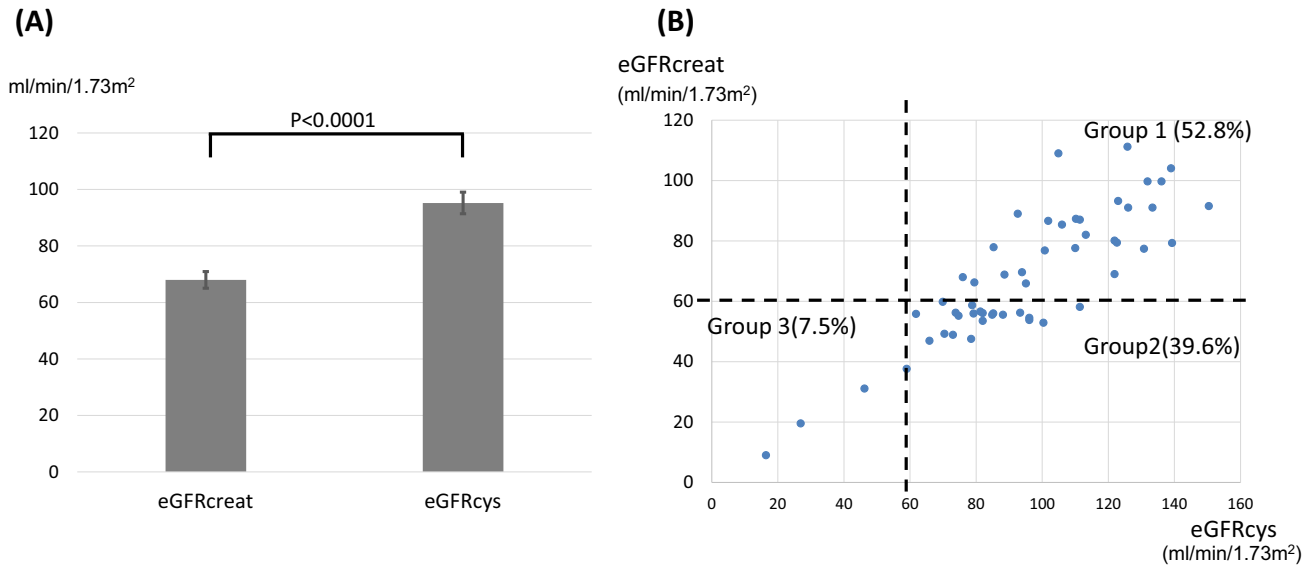

Fig. 1 Evaluation of renal function by eGFRcreat and eGFRcys. **a** Mean eGFRcreat and eGFRcys in all patients. The eGFRcreat was significantly lower than eGFRcys ($p < 0.0001$). Error bars represent standard errors. **b** Distribution of eGFRcreat and eGFRcys. Patients were divided into 3 groups: group 1, both eGFRs ≥60 ml/min/1.73 m^2; group 2, eGFRcreat <60 ml/min/1.73 m^2 but eGFRcys ≥60 ml/min/1.73 m^2; and group 3, both eGFRs <60 ml/min/1.73 m^2

diagnosed as stage 4 CKD. As shown in Fig. 1b, the prevalences of stage 3–5 CKD defined by eGFRcreat and eGFRcys were 47.2 and 7.5%, respectively. When a cut-off of 60 ml/min/1.73 m^2 was used, patients could be divided into 3 groups: group 1, both eGFRs ≥60 ml/min/1.73 m^2; group 2, eGFRcreat <60 ml/min/1.73 m^2 but eGFRcys ≥60 ml/min/1.73 m^2; and group 3, both eGFRs <60 ml/min/1.73 m^2. According to this grouping, 28 patients (52.8%) and 21 patients (39.6%) belonged to group 1 and group 2, respectively (Fig. 1b). Only 4 patients (7.5%) belonged to group 3. The mean eGFRcreat of patients belonging to group 2 was 54.4 ml/min/1.73 m^2 (46.9–59.8 ml/min/1.73 m^2), whereas that of eGFRcys was 82.2 ml/min/1.73 m^2 (61.8–111.4 ml/min/1.73 m^2).

We further analyzed eGFRcreat and eGFRcys according to total cisplatin dose and follow-up period after treatment. Those were compared between patients treated with total cisplatin dose below 400 mg/m^2 (31 patients) and above 400 mg/m^2 (22 patients). There was no significant difference in mean eGFRcreat (66.7 and 69.8 ml/min/1.73 m^2, respectively) and in mean eGFRcys (96.2 and 93.9 ml/min/1.73 m^2, respectively). Also no difference was observed in mean difference between eGFRcys and eGFRcreat (29.4 and 24.1 ml/min/1.73 m^2, respectively). When those were compared between patients with follow-up period of less than 7 years (27 patients) and 7 years or more (26 patients), again there was no significant difference in mean eGFRcreat (69.0 and 66.9 ml/min/1.73 m^2, respectively) and in mean eGFRcys (100.2 and 90.0 ml/min/1.73 m^2, respectively). In contrast, mean difference between eGFRcys and eGFRcreat was significantly higher in patients with the former patient group with shorter follow-up period compared to the latter group (31.2 and 23.1 ml/min/1.73 m^2, respectively; $p < 0.05$). However, correlation analysis between both eGFR estimations (eGFRcys–eGFRcreat) and follow-up period did not reveal significant time-dependency difference between the two values (supplementary figure 1, $r = -0.18$).

eGFRcreat, eGFRcys and GFR based on 24-h CrCl of cisplatin-treated TC patients and CKD patients with medical disease

GFR values (24-h CrCl) were available in 12 TC patients. All patients had eGFRcreat <60 ml/min/1.73 m^2. The median follow-up period of these patients was 65.0 months after completion of chemotherapy. For comparison, we evaluated GFR by 3 methods in 17 CKD patients with medical disease. As shown in Fig. 2a, in all TC patients, the eGFRcys values were higher than both eGFRcreat and GFR (24-h CrCl). The mean difference between eGFRcys and GFR (24-h CrCl) was 26.6 ml/min/1.73 m^2, but that between eGFRcreat and GFR (24-h CrCl) was only 0.15 ml/min/1.73 m^2. Figure 2b represents the mean values of both eGFR values in TC patients and patients with medical disease. In TC patients the mean eGFRcys was 71.0 ml/min/1.73 m^2, significantly higher ($p < 0.05$) than that of eGFRcys and GFR (24-h CrCl) at 44.3 and 44.4 ml/min/1.73 m^2, respectively. In contrast, in patients with medical disease, GFR values were almost identical among the 3 methods; the mean eGFRcys, eGFRcreat and GFR (24-h CrCl) were 36.7, 30.3 and 33.8 ml/min/1.73 m^2, respectively.

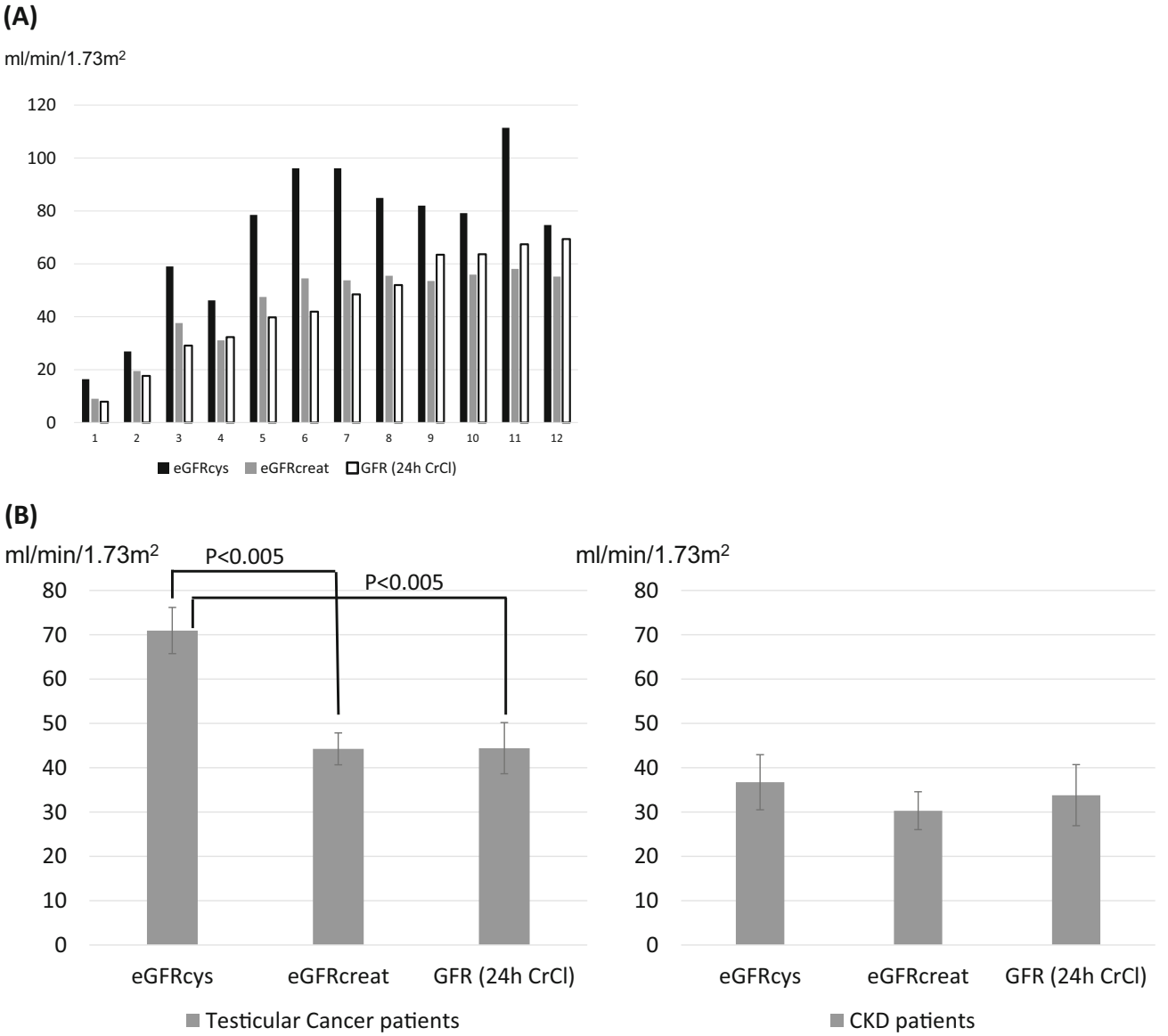

Fig. 2 eGFRcreat, eGFRcys and GFR (24-h CrCl) of cisplatin-treated TC patients and CKD patients. **a** Comparison of 3 parameters in each TC patient. eGFRcys was higher than eGFRcys and GFR (24-h CrCl) in all patients. Number represents each TC patient. **b** Mean eGFRcreat, eGFRcys and GFR (24-h CrCl) of TC patients and CKD patients. CKD patients including 7 kidney transplant recipients, 4 patients with nephrotic syndrome, 2 with Ig A nephropathy and 4 with miscellaneous diseases. The mean eGFRcys of TC patients was significantly higher ($p < 0.05$) than those of eGFRcys and GFR (24-h CrCl). Error bars represent standard errors

Prevalence of beta2-microglobulinuria and microalbuminuria among patients grouped by eGFRcreat and eGFRcys

Overall, 14 patients and 8 patients had significant beta2-microglobulinuria and microalbuminuria, respectively. As shown in Fig. 3a, beta2-microglobulinuria was observed in only 1 (3.6%) of the 28 patients belonging to group 1, whereas 10 (47.6%) of the 21 group 2 patients had beta2-microglobulinuria. The prevalence was significantly higher in the latter group ($p < 0.05$). Similarly, the prevalence of microalbuminuria tended to be higher in group 2 (19.0%) compared to group 1, but the difference was not significant. All patients belonging to group 3 had both beta2-microglobulinuria and microalbuminuria.

Discussion

Nephrotoxicity is a frequent long-term morbidity of chemotherapy for TC; previous studies have reported that 10–20% of TC survivors suffered from CKD [6–8]. CKD is a risk factor not only for renal failure, but also for cardiovascular events [22]. Cardiovascular disease as well as

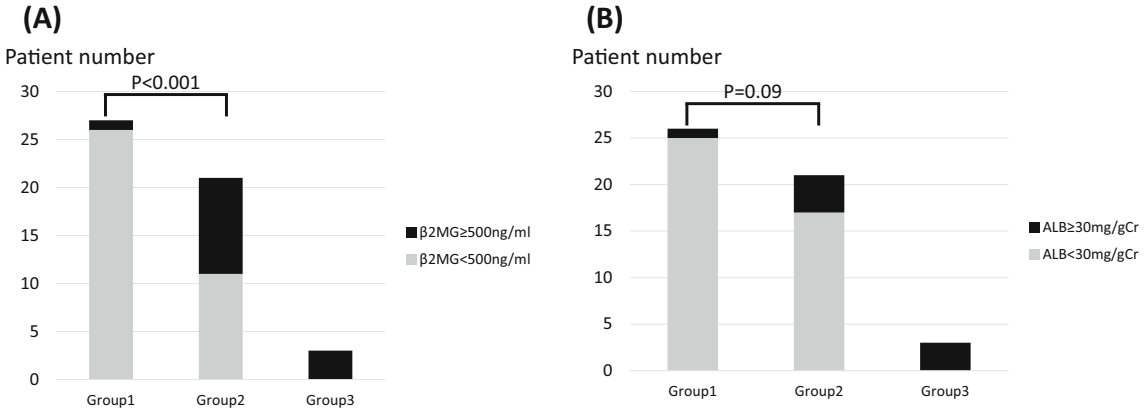

Fig. 3 Prevalence of beta2-microglobulinuria (**a**) and microalbuminuria (**b**) among patients grouped by eGFRcreat and eGFRcys. The prevalence of beta2-microglobulinuria was 47.6% in group 2 patients, significantly higher than that of group 1 patients (3.6%) ($p < 0.001$). The prevalence of microalbuminuria tended to be higher in group 2 (19.0%) compared to group 1, but the difference was not significant. Group 1, both eGFRs ≥60 ml/min/1.73 m^2; group 2, eGFRcreat <60 ml/min/1.73 m^2 but eGFRcys ≥60 ml/min/1.73 m^2; group 3, both eGFRs <60 ml/min/1.73 m^2. b2MG and ALB represent beta2-microglobulinuria and microalbuminuria, respectively

second malignancy is a well-known potentially fatal morbidity of TC survivors [2, 23]. Therefore, the accurate assessment of GFR is essential for survivors. In this regard, eGFRcys has shown promise as a less biased method than eGFRcreat in the general population. But, unexpectedly, the present study showed that eGFRcys is associated with a possible risk of overestimating GFR in survivors treated with cisplatin-based chemotherapy. As shown in Fig. 1, 47.2% of patients were diagnosed with stage 3–5 CKD based on eGFRcreat values, whereas the rate was limited to 7.5% when evaluated by eGFRcys. Several findings suggest the discrepancy was due to the overestimation of renal function by eGFRcys for survivors treated with cisplatin-based chemotherapy.

First, we focused on 21 patients showing eGFRcreat <60 ml/min/1.73 m^2 but eGFRcys ≥60 ml/min/1.73 m^2. The mean eGFRcreat of patients belong to this group was 54.4 ml/min/1.73 m^2, with a range of 46.9–59.8 ml/min/1.73 m^2. The kidney disease: Improving Global Outcomes (KDIGO) CKD guideline recommends measuring cystatin C (eGFRcys) in adults with eGFRcreat of 45–59 ml/min/1.73 m^2, because eGFRcys in this population leads to more accurate estimation of GFR [24]. However, in the present study, the mean eGFRcys of these patients was 82.2 ml/min/1.73 m^2, and half of them showed eGFRcys ≥80 ml/min/1.73 m^2.

Second, in all 12 TC survivors for whom 24-h CrCl was available, the eGFRcys values were higher than both eGFRcreat and GFR (24-h CrCl). The mean difference between eGFRcys and GFR (24-h CrCl) was 26.6 ml/min/1.73 m^2 while that between eGFRcreat and GFR (24-h CrCl) was only 0.15 ml/min/1.73 m^2. No significant discrepancy between eGFRcreat and eGFRcys was found in patients with medical disease; in fact, values of all three GFR methods were almost identical (Fig. 2b).

Third, in spite of favorable eGFRcys distribution (≥60 ml/min/1.73 m^2), the prevalence of beta2-microglobulinuria among patients in group 2 was as high as 47.6%. Beta2-microglobulinuria strongly suggests the presence of active and persistent tubular injury, the proposed pathogenesis of cisplatin-induced kidney injury. Also, 19% of group 2 patients had microalbuminuria. This finding supports the presence of clinically significant CKD in this patient group. The JNS guidelines recommend assessment of microalbuminuria to determine the prognosis of CKD. In TC survivors, Meinardi et al. also reported that 22% of patients had microalbuminuria [23].

Fourth, since we did not directly compare eGFRcreat and eGFRcys with inulin clearance, the possibility of underestimation of renal function by eGFRcreat is not completely ruled out. However, on this point, recently Funakoshi et al. reported that the Japanese eGFRcreat equation well correlated with inulin clearance in Japanese cancer patients after cisplatin treatment [25]. The authors also pointed out that eGFRcreat can overestimate but not underestimate renal function in patients with inulin clearance lower than 50 ml/min.

Several investigators have examined the correlation between serum cystatin C level or eGFRcys and other GFR estimation methods for assessment of cisplatin-induced nephrotoxicity [12–15]. However, the obtained results were rather contradictory. Two early studies demonstrated the superiority of the serum cystatin C level compared to the sCR level for detection of decreased 24-h CrCl or inulin clearance [12, 13]. In contrast, one study reported that there was no correlation between serum cystatin C level and sCR

level, eGFRcreat or CrCl calculated by Cockcroft–Gault after cisplatin administration [14]. But, in these studies, the serum cystatin C was measured during but not after chemotherapy. Therefore, changes of serum cystatin C of the studies were due to AKI rather than CKD. More recently, Oc et al. reported that there was no correlation between eGFRcys and 99mTc-DTPA clearance in 36 lung cancer patients treated with cisplatin-containing chemotherapy [15]. The authors evaluated 4 different eGFRcys formulas and compared to 99mTc-DTPA clearance. Before treatment, all cystatin C-based formulas were well correlated with 99mTc-DTPA clearance. In contrast, cystatin C-based formulas overestimated renal function compared to 99mTc-DTPA clearance after cisplatin chemotherapy. The 99mTc-DTPA clearance calculated by 2 different methods were 66.9 and 64.3 ml/min, whereas all 4 eGFRcys formulas showed higher GFRs with ranges between 73.6 and 99.0 ml/min. The findings are consistent with our results, and also suggested that there is a risk of overestimation not only in TC survivors but also in patients with other malignancy treated with cisplatin chemotherapy.

It is well described that serum cystatin C level is influenced by cell turnover states, such as hyperthyroidism, corticosteroid use, and presence of advanced malignancy [9]. However, subjects in the present study continued to show no evidence of TC or other malignancy with median follow-up period of 75.9 months after treatment. Also, no patient suffered from hyperthyroidism or active disease requiring corticosteroid treatment. Therefore, it is unlikely that TC or other diseases caused discrepancy between eGFRcreat and eGFRcys.

As shown in Fig. 3a, the prevalence of beta2-microglobulinuria in group 2 patients was high. Therefore, as another explanation, although not measured in the present study, there was a possibility that increase in the urinary excretion of cystatin C due to tubular injury might result in lower serum cystatin C levels in group 2 patients. But, this hypothesis cannot fully explain our results. As shown in Fig. 1b, the eGFRcys values were higher than both eGFRcreat in most of patients belonging to group 1. However, significant beta2-microglobulinuria was rarely seen in this patient group. Therefore, further investigation is needed to clarify the mechanism of discrepancy between eGFRcreat and eGFRcys.

To our knowledge, this is the first report regarding the reliability of eGFRcys in assessment of long-term nephrotoxicity in cancer survivors treated by cisplatin, but there are still two important limitations to the present study. First, the study population is relatively small. Second, we could not compare eGFRcys with inulin clearance, the gold standard for GFR assessment. Despite these limitations, our data showed that eGFRcys may overestimate renal function in TC survivors treated with cisplatin-based chemotherapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies were conducted (IRB approval number H24-23) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent as opt-out was obtained from all individual participants included in the study.

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