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Retrospective Analysis of Mortality Cases in Advanced and Metastatic Solid Tumors With Concurrent Prerenal Azotemia

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Abstract. *Background/Aim: A retrospective study of cases with metastatic or advanced solid tumors complicated with AKI (acute kidney injury) with prerenal azotemia. Patients and Methods: Criteria included: (1) advanced or metastatic solid tumors that led to mortality; (2) prerenal azotemia identified upon renal function evaluation and (3) BUN to Cr ratio (BCR)≥15. We also compared the outcomes of patients with BCR>20 with those of patients with BCR=15-20. Results: A total of 218 patients with solid tumors were enrolled. One hundred and forty (64%) and 78 (36%) patients had BCR>20 and 15-20, respectively. Before AKI occurrence, 136 (62%) had thromboembolic complications and 96 (44%) paraneoplastic syndromes. Median survival time was 1 week in all patients. Median survival time was statistically different between the groups with BCR15-20 and BCR>20 ($p<0.005$, log-rank test). Conclusion: Cancer patients with concurrent AKI and prerenal azotemia carry a very poor prognosis.*

Acute kidney injury (AKI) is defined as abrupt kidney damage resulting in the impairment of renal function within a few hours or days (1, 2). Understanding the pathogenesis of AKI during critical illness and developing therapeutic strategies for AKI based on the different possible etiologies are necessary (3). During AKI, cytokines are released from leukocytes and renal tubular cells in the injured kidney (4), and an inflammatory response occurs within the kidney after an episode of AKI (5). Prerenal azotemia, one of the causes of AKI, is defined as an increase in the blood concentration of nitrogen metabolism products, such as urea and creatinine (Cr) (6).

A blood urea nitrogen (BUN) to Cr ratio (BCR)>20 is used to distinguish prerenal azotemia and acute tubular necrosis, and high BCR patients have a higher hospital mortality (7). However, BCR is reported to have poor discriminatory ability in distinguishing prerenal AKI from intrinsic AKI (8). AKI is an important cause of morbidity and mortality in cancer patients, resulting in further complications (9, 10). Hence, AKI should be rapidly diagnosed and managed.

We designed a retrospective study including patients with metastatic or advanced solid tumors and with concurrent AKI with prerenal azotemia. We studied the clinical outcomes between two groups: one with a BCR 15-20 and the other with a BCR>20.

Patients and Methods

Patients. This retrospective case series was conducted between June 2008 and December 2019. Data were collected from 947 patients hospitalized in the oncology Department of the Chang-Gung Memorial Hospital. Because the data was mainly sourced from a single physician with expertise in urological cancers, most of these patients had urothelial carcinomas. Of these patients, 218 (23%) were documented to have prerenal azotemia.

The selection criteria included the following: 1) advanced or metastatic solid tumors resulting in mortality; 2) prerenal azotemia, as identified by renal function examination with the elevation of serum BUN and Cr levels; and 3) a BCR>15.

Ethics approval and consent to participate. The institutional review board/ethics committee determined that informed consent was not required. This study was approved by the Institutional Review Board (the "IRB") of Chang Gung Medical Foundation on 2020/02/09. IRB No.: 202000126B0.

Clinical and laboratory investigations. The patients often had thromboembolic complications and paraneoplastic syndromes. Common thromboembolism-associated complications included loss of consciousness and mental change, pulmonary venous obstructive syndrome, and iliofemoral venous obstruction or thrombosis. Due

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Key Words: Malignancy, acute kidney injury, prerenal azotemia, BUN to Cr ratio.

Table I. *Clinical characteristics of the 218 cancer patients with prerenal azotemia.*

Characteristics	No. of patients (%)
Age (years)	
Median (range)	68 (32-93)
Gender	
Male/Female	137/81
Primary tumor sites (N=218)	
Urothelial cancer	123 (56)
Non-urothelial cancer	95 (44)
BUN to Cr ratio (BCR)	218 (100)
>20	140 (64)
15-20	78 (36)
Associated with thromboembolic complications	136 (62)
Associated with paraneoplastic syndrome	96 (44)

to the difficulty in obtaining a definite diagnosis, cerebral thromboembolic complications could only be clinically suspected (11-13). Paraneoplastic syndromes included cachexia syndrome (a weight loss of >5% within six months, with reduced food intake and muscle wasting), neoplastic fever (tumor-related fever that responds well to the naproxen test) and hypercalcemia (11-13).

Laboratory examinations included complete blood counts (CBC), renal function test, D-dimer and C-reactive protein (CRP). D-dimer conducted using enzyme-linked immunosorbent assay. Severe anemia was defined as hemoglobin (Hb) levels less than 8 g/dl. Leukocytosis was defined as leukocyte counts greater than 15,000/μl and/or neutrophil counts greater than 12,000/μl. Leukopenia was defined as leucocyte counts less than 2,000/μl and/or neutrophil counts less than 1,000/μl. Thrombocytosis was defined as platelet counts greater than 400,000/μl. Thrombocytopenia was defined as platelet counts less than 100,000/μl. Presence of blast or immature myeloid cells was obtained from the differential counts of WBC. The elevation of BUN, Cr levels and BCR were greater than 21 mg/dl, 1.3 mg/dl and 15, respectively. For the purpose of the study of prerenal azotemia, we divided patients into two groups, those with BCR>20 and those with BCR 15-20. The cut off D-dimer and CRP values were 500 ng/ml and 5 mg/l, respectively. High D-dimer and CRP levels were defined as values greater than 5,000 ng/ml and greater than 50 mg/l, respectively.

Statistical methods. Continuous data (presented as mean±standard deviation) were used to determine the BUN, Cr, BCR, D-dimer, and CRP. The survival time was calculated from the occurrence of prerenal azotemia to death, and survival curves were determined using the Kaplan-Meier method. Significant differences between survival curves were measured using the log-rank test. The Chi-squared test was used to detect differences between subgroups, and a p-value<0.05 was considered statistically significant.

Results

The patients' clinical characteristics are shown in Table I. There were 218 patients with solid tumors enrolled. The population consisted of 137 men and 81 women, with an age range of 32 to 93 years.

There were 123 patients (56%) who had primary malignancies of the urothelium, including that of the bladder (n=77), renal pelvis (n=33), and ureters (n=13). The remaining 95 patients (44%) had the following cancer sites: lung (n=16), breast (n=9), renal (n=13), prostate (n=5), colorectum (n=9), pancreas (n=6), stomach (n=7), hepatobiliary tract (n=3), esophagus (n=7), head and neck (n=5), and others (n=10). There were 140 (64%) and 78 (36%) patients, respectively, who had BCR>20 and BCR=15-20, respectively. The mean values of BUN, creatinine, and BCR in the group that had BCR values greater than 20 were 64±36 mg/dl (30 mg/dl to 266 mg/dl), 2.2±1.2 mg/dl (1.3 mg/dl to 84 mg/dl), and 29.2±9.1 (20.1 to 52.9), respectively. The mean values of BUN, creatinine, and BCR in the other group (BCR=15-20) were 49±24 mg/dl (27 mg/dl to 128 mg/dl), 2.9±1.4 (1.4 mg/dl to 8.1 mg/dl) mg/dl, and 17.3±1.5 (15.1 to 19.8), respectively.

All patients had metastatic or advanced disease. There were 136 patients (62%) who had thromboembolic complications and 96 patients (44%) who had paraneoplastic syndromes. Common thromboembolic complications included cerebral thrombosis (n=79), pulmonary venous obstructive syndrome (n=57), iliofemoral vein obstruction/thrombosis (n=18), inferior venous cava thrombosis (n=6), sub-clavicular and jugular obstruction/thrombosis (n=2), and paraneoplastic pain (n=23). The common paraneoplastic syndromes were cachexia syndrome (n=94), hypercalcemia (n=6), and neoplastic fever (n=4).

The laboratory findings of the whole cohort and the BCR>20 and BCR=15-20 groups are shown in Table II. D-dimer was tested for 188 patients. The mean values were 6630±4128 ng/ml (170 mg/dl to >10,000 mg/dl) for all patients, 3267±2107 ng/ml (170 mg/dl to >10,000 mg/dl) for the group with a BCR>20 and 3402±1874 ng/ml (445 mg/dl to >10,000 mg/dl) for the group with a BCR=15-20. High D-dimer levels (>5,000 ng/ml) were found in 36% of the total cases, in 39% of cases with a BCR>20 and in 31% of cases with a BCR of 15-20. The CRP was assessed in 167 patients. The mean values were 229±173 mg/l (1 mg/dl to 403 mg/dl) for all of the patients, 110±80 mg/l (1 mg/dl to 362 mg/dl) for the subgroup with BCR>20, and 132±111 mg/l (1 mg/dl to 403 mg/dl) for the subgroup with a BCR 15-20. High CRP (>50 mg/l) was found in 70% of the total cases, in 71% of cases with a BCR>20, and in 70% of cases with a BCR 15-20. The CBC was tested in all patients. Severe anemia (Hb <8 g/dl) was detected in 38% of cases with a BCR>20 and in 54% of cases with a BCR of 15-20. Leukocytosis or neutrophilia (leukocytes >15,000/μl, neutrophil count >12,000/μl) was detected in 38% of cases with a BCR>20 and in 35% of cases with a BCR of 15-20. Leucopenia or neutropenia (leucocytes <2,000/μ/l, neutrophil count <1,000/μl) was found in 13% of cases with BCR>20 and in 15% of cases with a BCR of 15-20. Thrombocytopenia

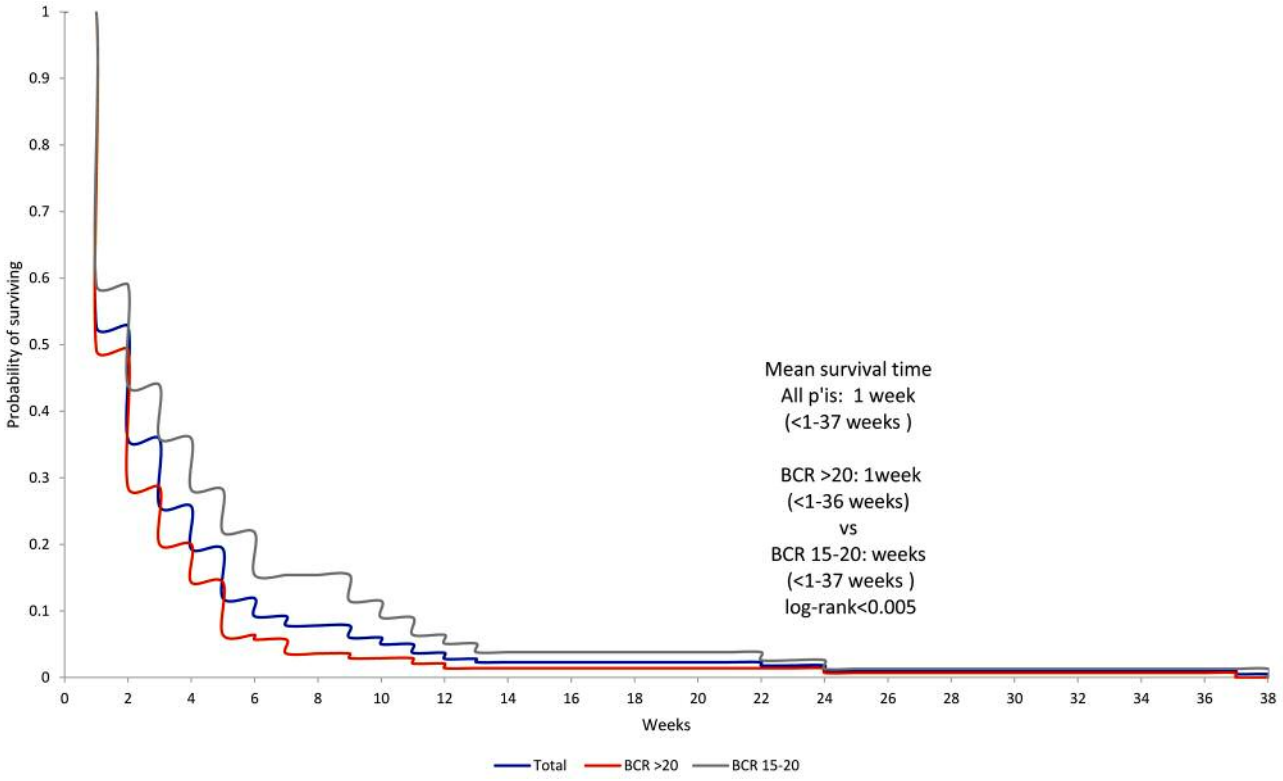

Figure 1. *Survival curve of all patients and those with BCR >20 and BCR 15–20 groups. Log-rank test comparing BCR >20 with BCR 15–20.*

Table II. *Laboratory findings from 218 cancer patients with prerenal azotemia: comparisons between patients with BUN to Cr ratio (BCR)>20 and BCR 15-20.*

Characteristics	Total patients (N=218)	BCR>20 (N=140)	BCR 15-20 (N=78)	*p*-Value
High D-dimer (≥5000 ng/ml)	63/175 (36)	43/111 (39)	20/64 (31)	0.32
High C-reactive protein (≥50 mg/l)	125/178 (70)	79/112 (71)	46/66 (70)	0.91
Severe anemia (Hb <8 g/dl)	95/218 (44)	53/140 (38)	42/78 (54)	0.028
Leukocytosis/neutrophilia (Leucocytes ≥15,000/μl/Neutrophil ≥12,000/μl)	80/218 (36)	53/140 (38)	27/78 (35)	0.63
Leucopenia/neutropenia (Leucocytes <2,000/μ/l/Neutrophil <1,000/μl)	30/218 (14)	18/140 (13)	12/78 (15)	0.60
Thrombocytopenia (Platelet <100,000/μl)	86/218 (39)	55/140 (39)	31/78 (40)	0.94
Thrombocytosis (Platelet ≥400,000/μl)	24/218 (11)	18/140 (13)	6/78 (8)	0.29
Presence of blasts or immature myeloid cells	120/218 (55)	69/140 (49)	51/78 (65)	0.031
Percentage of urothelial cancer	123/218 (56)	75/140 (54)	48/78 (62)	0.26

(platelet count <100,000/μl) was detected in 39% of cases with a BCR>20 and in 40% of cases with a BCR 15-20. Thrombocytosis (platelet count>400,000/μl) was found in 13% of cases with a BCR>20 and in 8% of cases with a BCR of 15-20. The presence of blasts or immature myeloid cells was detected in 49% of cases with BCR>20 and in 65% of cases with a BCR of 15-20. Urothelial cancers were present in 54% of cases with a BCR>20 and in 62% of cases with a BCR 15-20. By comparison, there was significantly more severe anemia (p=0.028) and a greater number of blasts or immature myeloid cells in cases with a BCR of 15-20 than in patients with a BCR>20 (p=0.031).

The median survival time for all patients was one week (range=<1-37 weeks). The median survival time was two

weeks (range=<1-37 weeks) in cases with a BCR 15-20 (range=<1-27 weeks) and one week (range=<1-36 weeks) in cases with a BCR>20. Survival time was statistically different between the two groups ($p<0.005$, log-rank test; Figure 1). There were 111 patients (51%), comprising 71 (51%) cases with a BCR>20 and 40 (51%) cases with a BCR 15-20, that had septicemia or infections as complications. The pre-death status identified in cases with BCR>20 and BCR=15-20 were predominantly a loss of consciousness [132 (94%), 8 (6%)] or respiratory failure [71 (91%), 7 (9%)], respectively.

Discussion

Cancer patients are at high risk for the development of AKI (14-19), which is related to the production of inflammatory cytokines and results in an increased mortality rate (19). In this study, the cancer patients that had concurrent AKI died in a very short time, and the mean survival time was only one week. Production of inflammatory cytokines can be due to cancer itself or to responses of the patients to invasive procedures, therapies, or infections (11, 20). Similarly, AKI in cancer patients can be secondary to cancer itself, driven by reactions of patients to bacterial infection, chemotherapy, or surgery (14-16). Half of our cases developed AKI due to other complications, such as septicemia or infection. As recurrent AKI is common in patients who have already been hospitalized with AKI, and because AKI is associated with an increased rate of death (21, 22), there is a need for clinicians to quickly identify risk factors and generate appropriate management plans (18).

Increased production of inflammatory cytokines can result in thromboembolic complications, cancer cachexia, and tumor progression, which result in poor prognoses (11, 12). In our study, before the onset of AKI, over 60% of patients had thromboembolic complications; of these, cerebral thrombosis and pulmonary venous obstructive syndrome were the most common (11, 12). Over 40% of patients had paraneoplastic syndromes, of which cancer cachexia was the most common. The levels of D-dimer were more than 5000 ng/ml in 36% of patients, and the CRP values were over 50 mg/l in 70% of patients. Elevated D-dimers and CRP values are indicators of venous thrombosis, are associated with increased levels of cytokines, and are predictors of a poor prognosis (23, 24).

A high BCR can be the result of high BUN, low creatinine levels, or both, although an increase in the ratio may also be due to a decrease in the blood flow to the kidneys and this may be more useful as a prognostic indicator of mortality (7). However, previous studies have shown that BCR fails to distinguish between prerenal and intrinsic AKI (25). In our study, the median survival time was worse in cases with BCR>20 than in cases with BCR 15-20. The higher BCR was probably related to an increased production of inflammatory cytokines, resulting in decreased renal blood flow. These consequences can accelerate thromboembolic complications, such as cerebral thrombosis (20).

In people who have cancer, anemia may be caused by inflammation, blood loss, or cancers that affect or spread to the bone marrow. Cancer treatments such as chemotherapy and radiation therapy may also cause or worsen anemia.

Anemia, leukocytosis, thrombocytosis, thrombocytopenia and the presence of immature myeloid cells and blasts in peripheral blood smears can be related to inflammatory cytokines and thromboembolic complications of the treatment of cancer patients (26-31). In our study, a more severe anemia and an increased number of blasts and immature myeloid cells characterized cases with BCR 15-20. We suspect that these symptoms were not related to the onset of AKI. However, we suggest that high BCR is related to an increased production of inflammatory cytokines and can promote cancer mortality.

Our study has several limitations. First, the data was collected retrospectively from cases in a single center. Second, cytokine levels were not measured in these patients. Finally, mental status changes and altered consciousness related to thromboembolic complications were seldom proved by imaging studies. All of these factors contributed to a limitation in data analysis.

Conclusion

Cancer patients with new-onset AKI with prerenal azotemia have a poor prognosis. The prevention of the acute inflammatory process and minimization of the risk of thrombosis and thromboembolic complications due to the response of patients to invasive procedures, therapies, or infections, are needed in therapeutic management.

Conflicts of Interest

The Authors declare that they have no competing interests in regard to this study.

Authors' Contributions

LT-Y collected and analyzed data and wrote the manuscript, LC-C offered the case, collected and analyzed data and wrote the manuscript.

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