Original Study

Impact of Perioperative Allogenic Blood Transfusion on Survival After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

Michael Rink,[1] Armin Soave,[1] Roland Dahlem,[1] Atiqullah Aziz,[1,2] Fahmy Al-Sayed,[3] Sven Peine,[4] Oliver Engel,[1] Luis A. Kluth,[1] Arnulf Stenzl,[3] Maximilian Burger,[2] Shahrokh F. Shariat,[5] Margit Fisch,[1] Hans-Martin Fritsche,[3] Georgios Gakis[3]

Abstract

The present retrospective multicenter study analyzed the effect of perioperative blood transfusions (PBTs) on the outcomes in 285 patients with upper tract urothelial carcinoma who had undergone radical nephroureterectomy (RNU). We found that patients receiving PBTs had inferior survival compared with that of patients without PBTs. Future investigations should focus on optimization of preoperative hemoglobin levels, surgical accuracy, and anesthetic management of RNU.

Background: Preoperative anemia is an independent predictor for unfavorable outcomes in patients with upper tract urothelial carcinoma (UTUC) who undergo radical nephroureterectomy (RNU). The effect of perioperative blood transfusion (PBT) on survival, however, has been insufficiently investigated. We investigated the impact of PBT on the outcomes of patients UTUC treated with RNU. **Patients and Methods:** We analyzed the data from 285 patients with UTUC who had undergone RNU at 3 German academic institutions. PBT administration was analyzed as a dichotomous variable (administered vs. not administered) and the number of PBT units as a continuous and categorical variable (0 vs. ≤ 2 vs. > 2). Cox regression models were used to analyze the impact of PBT on disease recurrence and survival. **Results:** A total of 81 patients (28.4%) had received a PBT with a median number of 2 U (interquartile range, 2-4). The administration of PBT was associated with advanced tumor stage, higher tumor grade, and preoperative anemia ($P \leq .049$ for all). At a mean follow-up of 52 months, PBT and an increasing number of PBT units were significantly associated with inferior overall survival ($P \leq .025$). On multivariable analyses adjusted for established UTUC outcome prognosticators, PBT was significantly associated with inferior overall survival (hazard ratio, 1.6; 95% confidence interval, 1.055-2.428; $P = .027$). **Conclusion:** PBT is an independent risk factor for worse overall survival in patients with UTUC treated with RNU. Continued efforts are warranted to optimize patients' preoperative hemoglobin level, surgical accuracy, and anesthetic management of RNU to reduce the necessity for PBTs.

Clinical Genitourinary Cancer, Vol. 14, No. 1, 96-104
Keywords: Anemia, Perioperative blood transfusion, Prognosis, Upper urinary tract, Urothelial cancer

Introduction

Although some patients with upper tract urothelial carcinoma (UTUC) have durable oncologic outcomes after extirpative surgery, others die of UTUC, especially once the disease has recurred.[1] Radical nephroureterectomy (RNU) is the reference standard treatment of patients with a normal contralateral kidney for high-grade

M. Rink and A. Soave contributed equally to this work.

[1]Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2]Department of Urology, Caritas St. Josef Hospital, University of Regensburg, Regensburg, Germany
[3]Department of Urology, University Hospital Tübingen, Tübingen, Germany
[4]Institute of Transfusion Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[5]Department of Urology, Medical University Vienna, Vienna, Austria

Submitted: Aug 18, 2015; Revised: Sep 27, 2015; Accepted: Oct 6, 2015; Epub: Oct 20, 2015

Address for correspondence: Michael Rink, MD, FEBU, Department of Urology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52 Hamburg D-20246, Germany
E-mail contact: mrink@uke.de

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.10.003

and/or invasive tumors of the renal pelvicaliceal system and ureters.[2] Although the surgical and medical management has improved during previous decades, RNU is still a cause of significant complications and morbidity for many patients.[3] Approximately one fifth of patients with UTUC who undergo RNU require administration of a perioperative blood transfusion (PBT).[4]

PBT has been suggested to be a risk factor for unfavorable oncologic outcomes in UTUC and various other malignancies[5,6] owing to a potential immunosuppressive effect evoked by the large amounts of antigens in transfused allogenic blood products. For different urologic malignancies treated with extirpative surgery with a relative high rate of PBTs (eg, prostate cancer,[7] renal cell cancer,[8] or urothelial carcinoma of the bladder[9,10] [UCB]), conflicting findings have been reported regarding the association of PBT and oncologic prognosis. Nevertheless, assessing the association of PBT with cancer control and survival remains important, because it could help to optimize patient management and thus potentially affect the outcomes.

Therefore, the aim of the present study was to evaluate the effect of PBT on the oncologic features and survival of patients with UTUC who underwent RNU. We hypothesized that the administration of PBTs would be associated with unfavorable outcomes comparable to those of other urologic cancers.[8-10]

Patients and Methods

Patient Selection

The study design has previously been described in detail.[11] In brief, the present study was retrospective and performed with the approval and oversight of the institutional review board at each institution, with all participating sites providing the necessary data-sharing agreements before initiation. We collected UTUC data from 3 German academic centers and combined the data sets in a computerized database. After the identification and resolution of any data inconsistencies, the database was frozen in 2012 before analysis.

A total of 348 patients with UTUC underwent RNU with a curative intent from 1992 to 2012. Patients with a history of radical cystectomy for treatment of muscle-invasive or high-risk non–muscle-invasive UCB were excluded from the present study (n = 11). In addition, 34 patients were excluded from the analysis because of missing clinicopathologic or follow-up data, 1 patient was excluded because of neoadjuvant chemotherapy, and 17 patients with missing preoperative hemoglobin levels or data on perioperative blood transfusion were excluded. Thus, complete data were available for 285 patients with UTUC, who constituted the study cohort.

RNU was performed according to the previously described standard.[11] Hilar or regional lymphadenectomy was generally performed in patients with suspicious lymph nodes on preoperative imaging or with suspicious intraoperative findings.[12] The indication and extent of lymphadenectomy performed was at the discretion of the individual surgeon. Tumor multifocality was defined as the synchronous presence of $\geq$ 2 pathologically confirmed tumors in any location (renal pelvicaliceal system or ureter, or both).[13] No patient received preoperative systemic chemotherapy or perioperative radiotherapy. Adjuvant chemotherapy (89% platinum based) was administered to 48 patients (16.8%) at the investigators' discretion according to evidence of advanced disease stage, performance status, renal function, and patient desire.

The administration of a PBT and the number of units transfused was recorded from the medical record review. PBT was defined as transfusion of allogenic red blood cells during RNU or postoperative hospitalization. Administration of a PBT was at the discretion of the treating physicians, without a standardized intra- or postoperative threshold used at each institution. Transfusion of other blood products was not recorded. A regular blood evaluation, including hemoglobin levels, was performed at each institution at the first day of the patients' hospitalization, generally 1 to 3 days before RNU. Preoperative anemia was defined in white male patients aged $<$ 60 years as a hemoglobin level of $\leq$ 13.7 g/dL and in white male patients aged $\geq$ 60 years as $\leq$ 13.2 g/dL. In white female patients of all ages, the threshold for anemia was defined as $\leq$ 12.2 g/dL.[11,14]

Pathologic Evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. The tumors were staged according to the 2010 American Joint Committee on Cancer TNM classification[15] by genitourinary pathologists. All patients had urothelial carcinoma without a pure variant histologic type.[16] The tumor grade was assessed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus classification.[17] The histopathologic assessment determined whether concomitant carcinoma in situ was present, the tumor architecture (papillary or sessile according to the predominant feature of the index lesion[18]), the presence of tumor necrosis (defined as the presence of microscopic coagulative necrosis in $>$ 10% of the tumor[19]), and the presence of lymphovascular invasion (LVI; defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls[20]).

Follow-Up Regimen

Patients were generally followed up every 3 to 4 months for the first 2 years after RNU, every 6 months from the third through the fifth year, and annually thereafter. The follow-up examination consisted of history, physical examination, urinary cytology, and cystoscopic evaluation of the urinary bladder. Computed tomography (CT) of the abdomen, including evaluation of the contralateral upper urinary tract, and chest radiography were generally performed semiannually or when clinically indicated. Additional imaging studies, including bone or brain scans, chest CT scans, and/or magnetic resonance imaging, were performed when clinically indicated.

Disease recurrence was defined as tumor relapse in the operative field, regional lymph nodes, and/or distant metastasis. Urothelial carcinoma developing in the bladder or contralateral upper tract was considered metachronous tumor and not coded as disease recurrence. The cause of death was determined by the treating physician, by medical record review corroborated by the death certificate, or by the death certificate alone.[21] All patients who had a code indicating they had died of cancer had had previous disease recurrence. Perioperative mortality was defined as any death within 30 days of surgery or before discharge. Perioperative mortality was censored at death for the cancer-specific survival analyses.