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Perioperative chemotherapy for urothelial carcinoma of the upper urinary tract: A systematic review and meta-analysis

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ABSTRACT

Introduction: Upper tract urothelial carcinomas are rare malignancies with differences in anatomy and biology requiring therapeutic strategies that differ from bladder cancer. The role of perioperative systemic therapy in this disease remains uncertain with limited data to support its use. A systematic review of the literature and meta-analysis was therefore undertaken to provide more information and guide clinical practice.
Methods: A literature search was performed using Embase and Medline databases with additional searches performed manually using terms associated with upper tract urothelial malignancies. Data was extracted from studies of patients that underwent nephrouretectomy for the management of upper tract urothelial carcinoma and received either neoadjuvant or adjuvant systemic therapy. Overall survival (OS), disease-free survival (DFS), and cancer-specific survival (CSS) were summated and analyzed using Cochrane Revman software Version 5.3.
Results: There were 13 comparative studies and no randomized studies identified for data extraction; 11 adjuvant and 2 neoadjuvant with 1170 patients receiving perioperative systemic therapy and 3472 controls that did not. Perioperative chemotherapy was associated with improved OS (HR 0.75, 95%CI 0.57–0.99), DFS (HR 0.54, 95%CI 0.32-0.92), and CSS (HR 0.69, 95%CI 0.42–1.15).
Conclusions: The available data suggests that perioperative systemic therapy is associated with improved survival in patients with upper tract urothelial cancer.

1. Introduction

The upper tract urothelial cancers (UTUC) arise from the urinary pelvis or ureters that have different embryologic, anatomic and biological attributes from lower tract urothelial malignancies that could result in important differences in clinical behavior and therapeutic outcomes. These differences may also result in difference in response to radiation and chemotherapy.

The renal pelvis and ureter arise from the mesonephric duct integrating into the renal medulla proximally and distally the bladder. These tissues have susceptibility to microsatellite instability associated with familial non-polyposis colorectal cancer and expression of substances within the extracellular matrix that are distinct from the urothelium of the urinary bladder (Riedel et al., 2005).

The clinical relevance of these differences is suggested by the results of a recent large randomized study comparing two chemotherapy regimens in the palliative setting yielding discordant results for upper and lower tract urothelial cancers (Bellmunt et al., 2012).

The accepted management of UTUC and muscle invasive urothelial bladder cancers is surgical consisting of nephroureterectomy and radical cystectomy respectively. Surgery alone is associated with a high risk of recurrence and 5 year survival rates of less than 50% (Sternberg, 2006) motivating the investigation of perioperative chemotherapy in the hope these strategies would provide for better outcomes.

The perioperative regimens studied are almost exclusively cisplatin and carboplatin based and have been utilized in both the neoadjuvant and adjuvant settings. The most commonly used are MVAC or variants of this regimen (methotrexate, vinblastine, doxorubicin, cisplatin) and GC (gemcitabine, cisplatin). These platin based regimens present challenges in patient populations with UTUC and bladder cancer as these populations are often older with significant renal impairment exacerbated in the adjuvant setting when nephroureterectomy has been

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undertaken. Febrile neutropenia also represents a significant and potentially fatal treatment limiting toxicity. This has led to caution in accepting the role of perioperative chemotherapy in the management of these diseases.

The management of patients with muscle invasive urothelial malignancies of the urinary bladder has been clarified by recent meta-analyses of neoadjuvant chemotherapy and for adjuvant chemotherapy in the post cystectomy setting. These studies do demonstrate an absolute 5-year survival benefit in the 5–15% range (Booth et al., 2014; Cl et al., 2008; Vale, 2003). This has resulted in increased acceptance of neoadjuvant or adjuvant chemotherapy as a standard of care in the management of muscle invasive bladder cancer. The role of radiation therapy is less clear but there is increasing evidence for concomitant chemotherapy and radiation therapy in bladder preservation strategies (Coppin et al., 1996; El-Taji et al., 2016; James et al., 2012; Lagrange et al., 2011).

The extrapolation of this data to the management of upper tract urothelial malignancies is an area of controversy. There is evidence to suggest that unlike bladder cancer, the survival of patients with UTUC may actually be decreasing over time (S. P. Porten et al., 2013). There are no randomized clinical trials and treatment decisions are dependent on expert opinion with attendant limitations and variation in practice (Sackett, 2000). A systematic review of the available information and query of the data bases available was undertaken to provide further information to guide practice for this less common subtype of urothelial malignancy. Specifically, we set out to investigate whether adjuvant or neoadjuvant chemotherapy improve overall survival for upper tract urothelial carcinoma in patients undergoing potentially curative surgery.

2. Methods

A systematic literature search was performed using Medline and Embase databases from inception to January 2017 including the terms ureter tumor, kidney pelvis, transitional cell carcinoma, drug therapy. Upper tract urothelial malignancies are not represented as a distinct entity within the keyword architecture of publication databases. The primary search stategy was developed after consultations with a librarian expert. Multiple searches were required with variation in terms adjuvant/neoadjuvant and additional drug-specific terms (Appendix 1). These searches were supplemented and verified by manual review of bibliographies and keyword searches using the search engine GOOGLE™. A large number of publications were retrieved and relevance ascertained see Fig. 1.

Study selection

The search was limited to comparative human studies. Only studies providing information on either overall survival, disease-free survival or cancer-specific survival were considered. Case reports were excluded. Studies analyzing cohorts with multiple disease sites other than upper tract urothelial carcinoma were also excluded. Only studies that provided survival information of both an intervention and control group allowing comparison were incuded.

2.1. Data extraction and statistical analysis

Data was extracted from the identified studies of adjuvant and neoadjuvant chemotherapy. Patient characteristics that were consistently published within studies were extracted and tabulated as descriptive statistics with performance status, tumor site and stage tabulated as percentages (Table 1). Survival data from the identified studies was extracted and summated for adjuvant and neoadjuvant chemotherapy (Tables 2 & 3) for adjuvant chemotherapy data extraction included OS with hazard ratios and confidence interval. Data was also extracted for DFS and CCS when this information was available. For the neoadjuvant studies only adequate information on overall survival was available for extraction. Estimates of Hazard Ratios (HR) were weighted and pooled using the generic inverse variance and random effect model. All meta-analyses were undertaken using Revman 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Statistical heterogeneity was assessed using the I^2 statistic.

The analysis of primary interest was the effect of perioperative chemotherapy on overall survival, secondary analyses of interest also undertaken were overall survival, disease-free survival and cancer specific survival for adjuvant therapy and overall survival for neoadjuvant therapy.

3. Results

After removal of duplicate publications, 625 records of possible interest were identified. The titles and abstracts were reviewed and 612 were eliminated (Fig. 1); 27 were duplicate records, 569 did not deal with the subject of perioperative chemotherapy for upper tract urothelial tumors or dealt with both bladder and upper tract tumors, 9 studies did not contain therapeutic information, 5 studies did not have an observation group for comparison and 2 were review articles leaving 13 publications available for data extraction. In the adjuvant chemotherapy analysis there were 11 included studies; in each of these studies, at least 75% of chemotherapy treated patients receiving Cisplatin or Carboplatin (Platin) based therapy. One study (Seisen et al) did not have specific information on treatment protocols but had inclusion criteria designed to exclude non-Platin based regimens. For studies providing information on neoadjuvant therapy, only 2 studies (Kitamura et al., 2012; Porten et al., 2014) contained information on overall survival and were included in the primary analysis of perioperative therapy and the secondary analysis for overall survival in neoadjuvant therapy. In both of these studies the majority of patients received Cisplatin-based chemotherapy. A third publication did not have information on overall survival (Matin et al., 2010).

There were no randomized trials and no prospective studies available; all information for summary analysis of adjuvant therapy came from 11 retrospective studies: 7 single-institution studies varying in size from 27 to 171 patients (Huang et al., 2015; Kawashima et al., 2012; Kim et al., 2015; Kim et al., 2013; Kwak et al., 2006; Lee et al., 2006; Soga et al., 2008) and 4 multi-institution studies varying in size from 308 to 3253 patients (Hellenthal et al., 2009; Seisen et al., 2017; Vassilakopoulou et al., 2011; Yafi et al., 2014). A total of 4501 patients were included for the adjuvant portion of the analysis, 1124 who underwent surgery followed by chemotherapy and 3377 controls who did not receive adjuvant chemotherapy.

One study (Seisen et al., 2017)) accounted for 62% of the patients for which data was available and the reported survival data had been adjusted with an inverse probability of treatment weighting.

The reporting of survival data also varied between studies. Five-year overall survival data was reported in 7 studies, disease-free survival in 3 studies and cancer-specific survival in 7 studies. For one study, (Vassilakopoulou et al., 2011) only disease-free survival could be estimated from the available information and contained a proportion of patients (20%) with metastatic disease. This study was excluded from all analyses. One small retrospective study (Kim et al., 2013) only reported cancer-specific survival. One study reported disease-free and cancer-specific survival (Kawashima et al., 2012). Two studies (Hellenthal et al., 2009; Huang et al., 2015) reported both overall 5-year and cancer-specific survival.

The 2 neoadjuvant studies included in the overall survival analyses were single institution with total of 141 patients, 46 of whom received neoadjuvant chemotherapy and 95 controls that did not receive neoadjuvant chemotherapy.

3.1. Perioperative chemotherapy

3.1.1. Overall survival

To examine the overall effect of chemotherapy in the perioperative