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Review article

The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UCC)

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Abstract

Objective: Urothelial cell carcinoma of the upper urinary tract (UUT-UCC) is a rare, aggressive urologic cancer with a propensity for multifocality, local recurrence, and metastasis. This review highlights the main chemotherapy regimens available for UUT-UCCs based on the recent literature.

Materials and methods: Data on urothelial malignancies and UUT-UCCs management in the literature were searched using MEDLINE and by matching the following key words: urinary tract cancer; urothelial carcinomas; upper urinary tract; carcinoma; transitional cell; renal pelvis; ureter; bladder cancer; chemotherapy; nephroureterectomy; adjuvant treatment; neoadjuvant treatment; recurrence; risk factors; and survival.

Results: No evidence level 1 information from prospective randomized trials was available. Because of its many similarities with bladder urothelial carcinomas, chemotherapy with a cisplatin-containing regimen is often proposed in patients with metastatic or locally advanced disease. Most teams have proposed a neoadjuvant or an adjuvant treatment based either on the combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) or on gemcitabine/cisplatin (GC). These regimens have been shown to prolong survival moderately. All recent studies have included limited numbers of patients and have reported poor patient outcomes after both neoadjuvant and adjuvant chemotherapy. Regarding metastatic UUT-UCCs, vinflunine has demonstrated moderate activity in these patients with a manageable toxicity. Interestingly, specific molecular markers [microsatellite instability (MSI), E-cadherin, HIF-1α, and RNA levels of the telomerase gene] can provide useful information that can help diagnose and determine patient prognosis in patients with UUT-UCC.

Conclusion: Chemotherapy with a cisplatin-containing regimen is often proposed in patients with metastatic or locally advanced disease. However, there is no strong evidence that chemotherapy is effective due to the rarity of the disease and the lack of data in the current literature. Thus, physicians must take into account the specific clinical characteristics of each individual patient with regard to renal function, medical comorbidities, tumor location, grade, and stage, and molecular marker status when determining the optimal treatment regimen for their patients. The ongoing identification of the oncologic mechanisms of this type of cancer might pave the way for the development of specific treatments that are targeted to the characteristics of each patient's tumor in the future.

Keywords: Chemotherapy; Urinary tract cancer; Prognosis; Recurrence; Urothelial carcinoma; Renal pelvis; Ureter

1. Introduction

Invasive urothelial cell carcinoma of the upper urinary tract has a poor prognosis. The 5-year survival rates for patients with stage T2 and T3 disease are of 73% and 40%, respectively, and the median survival for patients with stage T4 disease is approximately 6 months [1].

Surgery represents the only potentially curable therapeutic intervention for these patients. Nephroureterectomy with bladder cuff removal still is the standard of care [2] even though conservative treatment has comparable survival rates in patients with contraindications to radical surgery or small, low-grade lesions [3,4]. However, systemic recurrences are common in this disease [5], and it is therefore reasonable to consider periopera-

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tive chemotherapy in an effort to decrease a patient's risk of recurrence.

Urothelial tumors of the upper urinary tract, like those of the bladder, are considered to be relatively chemosensitive [6]. However, urothelial cell carcinomas of the upper urinary tract (UUT-UCCs) are rare, accounting for approximately 5% of all urothelial carcinomas with an estimated incidence of 1 to 4 cases per 100,000 individuals per year [7]. Because of the low frequency of these tumors, there are few reported series that have included more than 50 patients. In fact, most of the data regarding the clinical efficacy of chemotherapy in the neoadjuvant and adjuvant settings are based on outcomes from the treatment of bladder UCC.

The aim of this article is to critically review the currently available data regarding the role of chemotherapy in the treatment of UUT-UCC.

2. Methods

The literature search was done using the National Library of Medicine database (http://www.pubmed.gov). A MEDLINE search was performed with special emphasis on urothelial malignancies and UUT-UCCs management using combinations of the following terms: urinary tract cancer; urothelial carcinomas; upper urinary tract; carcinoma; transitional cell; renal pelvis; ureter; bladder cancer; chemotherapy; nephroureterectomy; adjuvant treatment; neoadjuvant treatment; recurrence; risk factors and survival. Articles were considered between 1990 and 2010. No evidence level 1 information from prospective randomized trials was available. We excluded case reports and articles not published in English. Due to paucity of randomized data, articles were selected for this review with regards to the following criteria: evolution of concepts, intermediate and long-term clinical outcomes, quality of the study, and relevance. Older studies were included selectively if historically relevant or in case of scant data in more recent publications.

3. Distinctive features of UUT-UCC

Although the mechanisms of carcinogenesis were initially thought to be similar throughout the urinary tract, recent epidemiologic data and genetic studies have suggested that differences exist between the UUT and lower urinary tract regarding tumor location and behavior [8].

The natural history of these tumors shows that 60% of UUT-UCCs are found to be invasive at the time of diagnosis compared with only 15% of bladder tumors. The vast majority of patients with invasive upper tract urothelial carcinoma have stage T3 or worse disease at the time of surgery and, if a lymph node dissection is performed, at least 20%–25% will have lymph node involvement at the time of surgery [9]. The worse prognosis of UUT-UCC is further reflected by mortality estimates, in which the mortality to incidence ratio for upper urinary tract disease is approximately 0.34 compared with 0.20 for lower tract urothelial cancer [10].

Interestingly, 30% of patients with UUT-UCC have a history of bladder UCC, but less than 2% of patients with bladder UCC have a history of UUT-UCC. Recurrence in the bladder or the contralateral urinary tract occurs in 30%–51% of patients with UUT-UCC [11]. The prognosis of patients with UUT-UCC differs based on the anatomic location of the tumor. For example, UCC of the ureter or the renal pelvis are not the same disease in terms of invasiveness and prognosis; ureteral UCC is associated with a higher local and distant failure rate than renal pelvis UCC [12].

These differences may be due in part to the difficulty of diagnosing early-stage urothelial cancer of the upper urinary tract and to differences in the underlying stroma and connective tissue that are present in the upper urinary tract. However, the genetic profiles of these 2 types of tumors also differ. For example, a high degree of microsatellite instability (MSI) is present in almost 25% of sporadic cases of UUT-UCC, but MSI is not found in bladder UCC [13].

4. Current guidelines for chemotherapy in patients with UUT-UCC

Randomized clinical trials comparing the outcomes of different treatment modalities in patients with UUT-UCC are not available. Therefore, the existing guidelines concerning the use of chemotherapy in UUT-UCC are poor and are based on expert opinion rather than on evidence-based data [14].

According to the EAU treatment guidelines, the chemotherapeutic regimens that are suggested for use in patients with UUT-UCC are the same as those used for bladder cancer and are indicated for patients with systemic disease as a palliative treatment [14]. Cisplatin-containing combination chemotherapeutic regimens have been the standard of care since the late 1980s. In metastatic patients with bladder cancer, methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) and gemcitabine/cisplatin (GC) regimens have been shown to prolong survival by 14.8 and 13.8 months, respectively [15]. Neither of the 2 combinations was proven to be superior to the other, but equivalence was not tested. The study yielded response rates of 46% and 49% for MVAC and GC, respectively. The major difference between the 2 combinations was related to toxicity, with GC being less toxic.

In patients with bladder cancer, the overall survival response rates differ with respect to patient-related factors and pretreatment disease-related factors [16]. Thus, physicians should take into account patients' prognosis, baseline health status (including their performance status and medical comorbidities), and their renal function (patients should have a creatinine clearance $>$ 60 mL/min) when deciding