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COMMENTARIES ON MEDICAL INNOVATIONS, NEW TECHNOLOGIES, AND CLINICAL TRIALS

COMMENTARY

Time to change the management of upper urinary tract urothelial carcinoma

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Due to the rarity of the upper urinary tract urothelial carcinoma (UTUC) and dearth of research, current literature lacked level 1 evidence and consisted of either retrospective or undersized/underpowered prospective studies. Recently Birtle et al. published the effects of adjuvant chemotherapy (AC) in UTUC in a phase III, open label, randomized controlled trial (RCT) (the POUT trial) [1]. The results of the clinical part of this trial were eagerly awaited, as this trial provides the first level 1 evidence for assessing the efficacy of systemic chemotherapy given to patients with locally advanced UTUC.

The standard of care for patients with UTUC, as recommended by the European Association of Urology (EAU) Guidelines, is nephroureterectomy followed by close monitoring [2]. We have solid evidence that primary urothelial carcinoma of the bladder (UCB) is sensitive to cisplatin-based chemotherapy. For UCB, it is also well known that not adjuvant, but neoadjuvant systemic cisplatin-based chemotherapy increases overall survival (OS) with 5% at 5 years resulting in a 14% decreased mortality risk (hazard ratio [HR]:0.86, 95% confidence interval [CI]:0.77-0.95, p:0.003) [3]. Even though most of the UTUCs and UCBs arise from transitional epithelium, they are accepted as two distinct entities, and are so-called 'disparate twins' not only because of clinico-pathological but also molecular differences [4, 5]. Nevertheless, research till now had shown that patients with UTUC may benefit from perioperative systemic chemotherapy [6, 7, 8]. Of three different systematic reviews and meta-analyses published during the last six years, the most recent one showed a significant effect of AC on disease-free survival (DFS) (HR:0.54, 95% CI:0.32-0.92, p:0.02), whilst no significant effects were observed for OS or cancer-specific survival (CSS) [8]. Failure of these studies to show any positive effect on hard oncological endpoints can be explained by the retrospective design with inherent biases, low number of included patients, and use of sub-standard chemotherapy regimens. The only prospective study, which assessed the efficacy of paclitaxel plus carboplatin in high-risk UTUC (≥pT3 or pN+), had no comparison arm [9].

At this point, the design of the POUT trial emerged to fulfill the lacking evidence for use of AC for

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UTUC. Patients who underwent radical nephroureterectomy and had pathologically confirmed pT2-4 pN0-3 M0 or pTany N1-3 M0 (provided all grossly abnormal nodes were resected) were randomized to either surveillance or four cycles of chemotherapy (gemcitabine + cisplatin [carboplatin for patients with glomerular filtration rate of 30–50 ml/min]) in a 1:1 allocation [1]. Even though it was first planned to recruit 345 patients, results of 260 patients in the intent-to-treat population fulfilled the primary endpoint (DFS), and led to the decision to close the trial early. A reduction of 55% in relative risk of disease recurrence or death (observed also in prespecified subgroups) and improved metastasis-free survival (secondary endpoint) were also observed, however, OS is not yet mature.

Although the POUT trial provides us evidence that AC can be added into the routine management of UTUC, there are some issues to be discussed. First, it can be underpowered. Second, the primary endpoint is not a hard endpoint. Instead of DFS, CSS would be a better endpoint. Third, both cisplatin and carboplatin are accepted. As it is already known from UCB that carboplatin is not as efficient as cisplatin, patients who have received carboplatin might have had worse outcomes, and therefore, this regimen might be useless.

It makes sense to hypothesize that neoadjuvant chemotherapy (NAC) would have a similar effect in UTUC as seen in UCB. Meta-analyses of several retrospective studies showed that NAC significantly improved the survival outcomes (OS, CSS, progression-free survival) of patients with locally advanced UTUC [6, 10]. Use of NAC can be more feasible for the majority of patients with UTUC as they can better tolerate a cisplatin-based chemotherapy with possible nephrotoxic side effects before nephroureterectomy. Moreover, there is a possibility of becoming ineligible to receive the planned chemotherapy (i.e., a non-cisplatin-based regimen instead) and/or dose reduction in the regimen due to loss of functioning renal mass. On the other hand, NAC has the disadvantages of overtreatment for some patients and risk of ineligibility or delay for surgical treatment. For this reason, we do need better staging with the help of novel imaging methods and/or molecular subtyping. At this point, the POUT trial may be of help as the translational part of this trial (POUT-T) aims to identify any diagnostic, prognostic or predictive biomarker by means of genomic, epigenetic and transcriptomic analyses [1]. This trial will also aim to search for any imaging biomarkers for better prediction of muscle invasiveness in preoperative computed tomography urograms.

Apart from systemic cytotoxic chemotherapy, patients with UTUC can benefit from novel treatments, such as immune checkpoint inhibitors (atezolizumab, pembrolizumab, nivolumab, durvalumab) and/or fibroblast growth factor receptor (FGFR) inhibitors (erdafitinib) given either in neoadjuvant or adjuvant setting. Until we see the results of a study for NAC with a similar design of POUT trial and experiment the efficacy of these novel treatment agents, AC can be implemented in the routine management of UTUC patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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