

POUT trial: Perioperative chemotherapy in upper tract urothelial carcinoma – A standard of care?

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SUMMARY

The Peri-Operative chemotherapy versus surveillance in upper Tract urothelial cancer (POUT)^[1] trial is a multicentric, Phase III, open-label randomized control trial, aimed to assess the efficacy of adjuvant chemotherapy (ACT) in selected upper tract urothelial carcinoma (UTUC) patients.

The trial recruited a total of 261 patients of age ≥ 16 years, diagnosed with nonmetastatic UTUC between June 2012 and November 2017, who underwent *en bloc* radical nephroureterectomy (RNU) with lymph node dissection (resection of radiographically or macroscopically enlarged nodes). Patients with predominant transitional cell carcinoma (TCC) histology, pathologically staged as either muscle-invasive or lymph node-positive disease and fit to receive ACT within 3 months of surgery were included in the study. They were randomized (1:1) to either surveillance (129) or ACT (132) group, and the arms were balanced for the platinum agent used, lymph node status, and surgical margins.

The chemotherapy group received four cycles of 3 weekly schedule of platinum-based chemotherapy. Gemcitabine (G, 1000 mg/m²) was administered on days 1 and 8 and either cisplatin (C, 70 mg/m², estimated glomerular filtration rate [eGFR] >50 mg/dl) or carboplatin (CR) (in patients with eGFR <50 and ≥ 30 ml/min) on day 1 of each cycle. Adverse events during chemotherapy were assessed with the Common Terminology Criteria for Adverse Events version 4.0, and dose modification was done accordingly. In the cisplatin group, if the eGFR fell to 50–69 mL/min, split dose of cisplatin was infused on 2 consecutive days, and if the eGFR fell to 30–49 mL/min, cisplatin was switched to carboplatin.

The recurrence of the disease was evaluated by either a plain X-ray or a computed tomography of the abdomen, pelvis, and thorax at 3-monthly intervals in the 1st year, 6-monthly up to 3 years, then annually up to 5 years and by check cystoscopy at every 6 months

for 2 years, then yearly till 5 years. The trial was designed to detect a hazard ratio (HR) of 0.65 in favor of ACT, equivalent to a 15% absolute improvement in 3-year disease-free survival (DFS), which corresponds to the available data for carcinoma bladder.

The median age of patients ($n = 260$, one denied consent) was 68.5 years. Out of the 260 patients, 245 (94%) had stage pT2–T3, 223 (91%) had stage N0, and 166 (64%) had eGFR ≥ 50 mL/min. Of the total 126 (two patients switched in from the surveillance group and seven switched out from the chemotherapy group) patients who were planned for chemotherapy (76 to gemcitabine cisplatin [GC] and 50 to gemcitabine carboplatin [GCR]), only 75% (95) completed four cycles (42 received GC and 53 received GCR). Thirty one patients discontinued chemotherapy, of which ten were attributed to treatment-related toxicity.

As a primary endpoint, the 3-year DFS estimates were 71% (95% confidence interval [CI]: 61–78) in the chemotherapy arm and 46% (95% CI: 36–56) in the surveillance arm, with an estimated absolute difference of 25% (95% CI: 11–38). At the median follow-up of 30.3 months, ACT significantly improved DFS (HR: 0.45, $P = 0.0001$). The median DFS was 29.8 months (interquartile range: 6.3–not reached; 95% CI: 13.6–in calculable) and was not reached in the surveillance and the ACT groups, respectively. There were 24 deaths in the chemotherapy arm and 38 in the surveillance arm. The participants who received ACT also had a lower risk of metastasis or death (HR: 0.48, log-rank $P = 0.0007$).

In the chemotherapy group, 44% (55/126) of the participants had Grade 3 or more treatment-related adverse events, which were managed effectively, and there were no treatment-related death. Global health was lower during and at 3 months of chemotherapy but resolved by 6 months.

Considering UTUC as a rare disease and the promising results of chemotherapy in DFS, the authors strongly recommend adjuvant platinum-based chemotherapy in muscle-invasive or node-positive disease.

COMMENTS

Urothelial carcinoma or TCC of the upper urinary tract is a relatively rare malignancy and accounts for only 5%–10% of all the TCCs.^[2] UTUCs are frequently diagnosed at a higher stage (up to 60% are muscle invasive at the time of presentation), are prone to recur, and carry a poorer prognosis than TCC of the bladder.^[3] Due to the rarity of the disease and a lack of large-scale trials, the role of chemotherapy in UTUC is primarily extrapolated from the management of bladder carcinoma. The role of platinum-based chemotherapy in neoadjuvant,^[4] adjuvant,^[5] and metastatic^[6] settings of TCC of the urinary bladder is well established and supported by Level I evidence. Still, only limited evidence is available to justify chemotherapy in UTUC, generated either from bladder cancer studies or from retrospective studies of UTUC.

Standard of care for the treatment of patients with high-risk (high-grade or invasive) UTUC is RNU with or without adjuvant or neoadjuvant chemotherapy, as per the preference of the treating urologists. The POUT trial is the largest randomized control trial published, evaluating the efficacy of gemcitabine–platinum-based chemotherapy in UTUC, and it provides Level I support for ACT in muscle-invasive or node-positive disease. However, the implications of these results, in general, should be viewed with caution. Even after randomization, there were more T2 patients in the chemotherapy group (44 vs. 30) and more T4 patients in the surveillance group (11 vs. 4). Due to the small sample size, these differences can have a bearing on the outcomes. Further, no uniform standard lymph node dissection template was used to detect lymph node metastasis. Although the therapeutic advantage of lymph node dissection in RNU remains a matter of further research, its prognostic value in predicting recurrence has been shown by some retrospective studies.^[7] A standard and uniform lymph node dissection in a trial setting is expected to provide a more comprehensive and accurate pathological staging information and may guide the use of ACT.

The subgroup analysis in the POUT trial indicates that more favorable results with ACT were seen in N0 patients as compared to N+ patients, which raises a concern regarding inadequate randomization and selection bias. The relative effects of cisplatin and carboplatin on the survival of patients remain unclear from this study and need a dedicated trial.

The overall survival (OS) data from the said trial are still awaited and is planned after 88 deaths or after a follow-up of at least 2 years of all the patients.

Although the POUT trial offers Level I evidence regarding the advantage of administering ACT following RNU in patients with locally advanced and/or node-positive UTUC, some issues remain unaddressed. The optimal setting (neoadjuvant vs. adjuvant) of perioperative chemotherapy, whether noncisplatin-based chemotherapy would be equally efficacious in the adjuvant setting, and the role of immunotherapy as a neoadjuvant or adjuvant therapy in UTUC needs further research. Considering the decrease in the global eGFR (relative contraindications of platinum-based chemotherapy) and a possible delay in the administration of chemotherapy after nephrectomy, neoadjuvant chemotherapy could be theoretically preferred over adjuvant chemotherapy. Still, a well-designed large randomized controlled trial is required to support this concept scientifically. The recently published meta-analysis of retrospective studies by Kim *et al.* showed that neoadjuvant chemotherapy improved OS, cancer-specific survival, and progression-free survival by 57%, 59%, and 45%, respectively, in locally advanced UTUC.^[8]

Due to the lack of reliability of radiological imaging to accurately diagnose and stage invasive UTUC preoperatively, as highlighted in the POUT trial, chemotherapy in adjuvant setting stands well-founded, and can be considered as the standard of care in the management of invasive UTUC (pT2–T4; N0–3; M0).

REFERENCES

1. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, *et al.* Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): A phase 3, open-label, randomised controlled trial. *Lancet* 2020;395:1268-77.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7-34.
3. Meng X, Chao B, Vijay V, Silver H, Margolin EJ, Balar A, *et al.* High response rates to neoadjuvant chemotherapy in high-grade upper tract urothelial carcinoma. *Urology* 2019;129:146-52.
4. Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, *et al.* Neoadjuvant chemotherapy for muscle-invasive bladder cancer: A systematic review and two-step meta-analysis. *Oncologist* 2016;21:708-15.
5. Leow JJ, Martin-Doyle W, Rajagopal PS, Patel CG, Anderson EM, Rothman AT, *et al.* Adjuvant chemotherapy for invasive bladder cancer: A 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol* 2014;66:42-54.

6. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, *et al.* Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602-8.
7. Fajkovic H, Cha EK, Jeldres C, Donner G, Chromecki TF, Margulis V, *et al.* Prognostic value of extranodal extension and other lymph node parameters in patients with upper tract urothelial carcinoma. *J Urol* 2012;187:845-51.
8. Kim DK, Lee JY, Kim JW, Hah YS, Cho KS. Effect of neoadjuvant chemotherapy on locally advanced upper tract urothelial carcinoma: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2019;135:59-65.


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