Uroscan

The grimacing face of adverse upper tract urothelial carcinoma can now POUT with adjuvant chemotherapy!

Sumit Mandal*

Department of Urology and Renal Transplant, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

*E-mail: dr9sumit@gmail.com

SUMMARY OF THE POUT TRIAL

This multicentric study,[1] conducted in the United Kingdom, enrolled patients with locally advanced (pT2-T4 N-any M0) and/or node-positive (pT-any N + M0) upper tract urothelial carcinoma (UTUC) within 3 months of radical nephroureterectomy (RNU), between 2012 and 2017. Eligible and fit participants with the WHO performance status 0–1 and GFR >30 were randomly assigned into two groups after RNU, having balanced for planned platinum agent, nodal status, margin involvement, and treating center. One group received four 21 day cycles of adjuvant gemcitabine (1000 mg/m^2 on day 1 and 8) with cisplatin (70 mg/m^2 if estimated glomerular filtration rate [eGFR] was >50 ml/min) or carboplatin (if eGFR 30–49 ml/min on day 1) starting within 90 postoperative days while the other were kept under surveillance only.

The primary endpoint was disease-free survival (DFS), whereas the secondary endpoints were overall survival (OS), metastasis-free survival (MFS), disease-specific survival (DSS), time to bladder second primary (TBSP), acute and late (6–24 months) toxicity (Common Terminology Criteria for Adverse Events, CTCAE v4), treatment compliance, and quality of life (QoL). All the patients were followed up as high-risk patients.

The trial,[2] despite aiming for 338 patients to detect 15% absolute improvement in 3-year DFS to obtain a hazard ratio (HR) of 0.65, was halted prematurely by the safety monitoring committee due to a significant improvement in observed DFS in the adjuvant arm. Therefore, the ITT analysis was done on 260 patients after 1 nonconsenting patient was excluded (131 chemotherapy vs. 129 surveillance) where the majority were node negative following lymph node dissection (~90%). In comparison between the surveillance and chemotherapy arms, 23% versus 28% of patients displayed pT2 disease, 68% versus 66% exhibited pT3 disease, with the rest having pT4 disease, respectively. The median follow-up was 65 months (interquartile range 60–84).

A clear benefit of adjuvant chemotherapy was seen with a marked improvement in 5-year DFS observed in the chemotherapy arm compared to surveillance (5-year DFS 62% vs. 45%; univariable HR, 0.55 [95% confidence interval (CI), 0.38–0.80], P = 0.001; multivariable HR, 0.58 [95% CI, 0.40–0.84], P = 0.004). Furthermore, the restricted mean survival time (RMST) for DFS was 72 and 54 months, respectively, with an 18-month improvement in the chemotherapy arm (95% CI, 6–30, P = 0.003).

Adjuvant chemotherapy did indicate an improvement in the OS (5-year OS 66% vs. 57%; univariable HR, 0.68 [95% CI, 0.46–1.00], P = 0.049; multivariable HR, 0.76 [95% CI, 0.51–1.12], P = 0.17) with RMST improvement of 11 months (78 vs. 67 months, 95% CI, 1–21, P = 0.036). The MFS and DSS also showed benefit of chemotherapy with 18 months (95% CI, 6–29, P = 0.002) improvement in RMST for MFS. Furthermore, adjuvant chemotherapy treated patients had lesser recurrence (47 vs. 71%), thereby requiring lesser subsequent systemic treatment (49 vs. 63%). On the contrary, chemotherapy could not bring a difference in TSPB (HR 0.93, 95% CI, 0.59–1.46, P = 0.75).

Fortunately, no difference in adverse events was found at all time frames, as was seen in the overall score and individual domains of QoL.

Thus, the Perioperative chemotherapy versus surveillance in upper Tract urothelial cancer (POUT) trial revealed a significant improvement in DFS, MFS, and DSS with a favorable trend in OS for adjuvant chemotherapy in locally advanced UTUC.

COMMENTS

The management of UTUC poses significant challenges due to its rarity, resulting in limited robust evidence-based guidelines which is why the authors should be applauded. RNU is now considered the standard treatment for high-risk UTUC, with the inclusion of platinum-based chemotherapy

either before (neoadjuvant) or after (adjuvant) surgery based on inferior levels of evidence.[3] The groundbreaking POUT trial represents a pivotal effort in the field of UTUC management bringing the first exciting level I evidence on the benefit of adjuvant chemotherapy administration after RNU in patients with locally invasive or node-positive UTUC.

Several questions remain unanswered,[4] including the optimal chemotherapy regimen, benefits across subgroups, and adjuvant versus delayed chemotherapy at relapse. Despite randomization, the pT stage distribution was uneven, and template nodal dissection was not consistently followed, potentially affecting the study's generalizability.

Encouragingly, the GFR requirement for cisplatin was lowered to 50 ml/min due to the disease's rarity and the treating physicians' expertise. We learnt not to be a racehorse with the blindfolds (of Galsky).[5] The adjuvant Gem-Carbo combination showed some benefit, even for patients with lower GFR.

We now have Level 1 evidence for adjuvant chemotherapy in UTUC management, but high-quality studies are needed to assess its neoadjuvant potential. While DFS was the primary endpoint, OS remains the ultimate measure of efficacy. In addition, immunotherapy, such as nivolumab, shows promise, emphasizing the need for tailored treatment approaches and further research.

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. Available from: https://www.thelancet.com/article/S0140673620304153/fulltext. Accessed on 19th May, 2024
2. Birtle AJ, Jones R, Chester J, Lewis R, Biscombe K, Johnson M, *et al*. Improved Disease-Free Survival With Adjuvant Chemotherapy After Nephroureterectomy for Upper Tract Urothelial Cancer: Final Results of the POUT Trial. Available from: https://ascopubs.org/doi/10.1200/JCO.23.01659. Accessed on 6th June, 2024
3. Rouprêt M, Seisen T, Birtle AJ, Capoun O, Compérat EM, Dominguez-Escrig JL, *et al*. European association of urology guidelines on upper urinary tract urothelial carcinoma: 2023 update. Eur Urol 2023;84:49-64.
4. Ranjan SK. POUT trial: Perioperative chemotherapy in upper tract urothelial carcinoma – A standard of care? Indian J Urol 2020;36:324-6. Available from: https://journals.lww.com/indianjurol/fulltext/2020/36040/pout_trial__perioperative_chemotherapy_in_upper. 18.aspx. Accessed on 3rd June, 2024
5. Galsky, Matt and Hahn, Noah and Rosenberg, J. and Sonpavde, Guru and Oh, William and Dreicer, Robert and Vogelzang, Nicholas and Sternberg, C. and Bajorin, D. and Bellmunt, J. (2011). Defining "cisplatin ineligible" patients with metastatic bladder cancer. Journal of Clinical Oncology. 29. 238-238. https://doi.org/10.1200/jco. 2011.29.7_suppl. 238. Accessed on 23rd June, 2024

Received: 03.03.2024, **Revised:** 07.06.2024,

Accepted: 11.07.2024, **Published:** 30.08.2024

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_87_24

How to cite this article: Mandal S. The grimacing face of adverse upper tract urothelial carcinoma can now POUT with adjuvant chemotherapy! Indian J Urol 2024;40:281-2.