Bladder Cancer 6 (2020) 219–221
DOI 10.3233/BLC-200005
IOS Press

Clinical Trials Corner

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Received 15 May 2020
Accepted 18 May 2020
Pre-press 9 June 2020
Published 11 June 2020

Dear Readers,

In this issue, we highlight two trials that redefine the treatment of upper tract urothelial cancer. First, is the OLYMPUS trial that establishes efficacy of mitomycin delivered via a novel delivery vehicle for the treatment of low-grade upper tract urothelial cancer. This led to the FDA approval of this treatment and the new trade name of JELMYTO. Second is the POUT trial demonstrating the benefit of adjuvant chemotherapy after nephroureterectomy for upper urinary tract urothelial cancer. In the future, please reach out to us directly in order to highlight any specific clinical trials at pkagarwal@uchicago.edu or cns9006@med.cornell.edu and/or at BLC@iospress.com.

Sincerely,

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Study Title: A Phase 3 Multicenter Trial Evaluating the Efficacy and Safety of MitoGel™ on Ablation of Upper Urinary Tract Urothelial Carcinoma (The OLYMPUS Study – Optimized DeLivery of Mitomycin for Primary Upper Tract Urothelial Carcinoma Study)[1]

Clinicaltrials.gov identifier: NCT02793128

Sponsor: UroGen Pharma Ltd.

Enrollment: 71

Rationale: Unlike bladder urothelial carcinoma, upper tract urothelial carcinoma (UTUC) has not been successfully treated with instillation therapy with chemotherapy or immunotherapy. Although some case reports describe instillation therapy into the upper urinary tract delivered through nephrostomy tubes, there has not been a reliable and convenient method of delivery until now. This trial uses a novel formulation of mitomycin C (MitoGel, now named JELMYTO) that can be instilled in a liquid form which can solidify at body temperature into a gel that can allow dwell times of several hours in the upper urinary tract. Mitomycin C is an alkylating agent that inhibits the transcription of DNA into RNA thereby preventing protein synthesis and inhibiting growth of cancer cells. It has shown to be effective in urothelial cancer of the bladder.

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ISSN 2352-3727/20/$35.00

Study Design: This was a prospective, multicenter open-label single-arm trial evaluating the safety, efficacy, and tolerability of MitoGel instilled into the upper urinary tract of patients with non-invasive low-grade (LG) UTUC. Patients had to have at least one measurable papillary tumor. Patients were treated once weekly for 6 weeks by retrograde instillation. Safety and Efficacy was evaluated approximately 5 weeks following the last instillation, roughly 11 weeks after enrollment, by direct inspection of the upper tract, biopsies of any tumors, and upper tract washed urine cytology. Patients who achieved a CR at 3 months were treated with monthly maintenance therapy for a total of 11 instillations or up to the first recurrence whichever came first.

Endpoints: The primary endpoint was the complete response (CR) rate at 3 months. Secondary endpoints included the CR rate at 12 months. The mitomycin C level was also evaluated in the plasma of a subgroup of the patients.

Results: This study demonstrated a CR rate of 59% (42 patients) at 3 months. Nineteen of these patients (46%) maintained a CR at 12 months. The most frequent adverse events included ureteric stenosis (44%), urinary tract infection (32%), hematuria (31%), flank pain (30%), and nausea (24%). Of note, of the patients who developed ureteric obstruction, 51% had some level of persistent obstruction.

Comments: This is the first trial exclusively for upper tract urothelial cancer and it establishes the first FDA-approved therapy in this rare, "orphan," disease. In addition, the therapy was effective in patients without complete resection/ablation of existing papillary tumors. However, the response rate was only durable at 12 months in approximately 20% (14 of 71) of the patients and was limited to only those patients with LG disease. Given the inaccuracies with grading and staging of upper tract urothelial cancer based on small volume biopsies, it is also conceivable that some patients with high grade disease may be inadvertently treated with this approach which may not be effective. Nevertheless, this trial has paved the way for localized therapies for UTUC.

Study Title: A Phase III Randomised Trial of Peri-Operative Chemotherapy Versus Surveillance in Upper Tract Urothelial Cancer (POUT Study)[2]

Clinicaltrials.gov identifier: NCT01993979

Sponsor: Institute of Cancer Research, United Kingdom

Enrollment: 261

Rationale: The benefit of peri-operative chemotherapy for urothelial cancer of the bladder is well established for neoadjuvant therapy and less so for adjuvant therapy due to the difficulties in accrual to many of these trials. Although UTUC is related to urothelial cancer of the bladder, the role of chemotherapy and the proper sequencing of surgery with chemotherapy in UTUC is largely unknown and frequently extrapolated from the management of bladder cancer. This trial specifically evaluates the impact of adjuvant chemotherapy given after nephroureterectomy for high grade UTUC.

Study Design: This was a phase III, multi-center open-label randomized controlled trial in which patients who had undergone nephroureterectomy for UTUC, with pT2-T4, N0 disease or pTany N1-3 M0 disease, and fit for adjuvant chemotherapy, were randomized (1:1) to either four cycles of platinum-based adjuvant chemotherapy or surveillance. Patients with microscopically positive margins on pathology were permitted as long as all gross disease was resected. Chemotherapy consisted of four 21-day cycles of gemcitabine-cisplatin, however, in patients with GFR 30-49 mL/min, carboplatin was substituted for cisplatin and was initiated within 90 days of surgery.

Endpoints: The primary endpoint of the trial was disease-free survival (DFS) at three years. The secondary endpoints included overall survival, metastasis-free survival, incidence of bladder second primary tumors, incidence of contralateral primary tumors, acute and late toxicity, treatment compliance, and quality of life.

Results: Ultimately, 132 patients were assigned chemotherapy and 129 were assigned surveillance. Adjuvant chemotherapy significantly improved DFS (HR = 0.45, 95% CI 0.3-0.68, p=0.0001) at a median follow-up of

30.3 months with 3-year DFS estimates of 71% (chemotherapy) vs. 46% (surveillance). In addition, the metastasis-free survival rate at two years was 74% vs. 60% for chemotherapy vs. surveillance patients (p=0.002), respectively. However, overall survival was not significantly different between the groups in the early published analysis. On subset analysis, chemotherapy did not demonstrate a benefit in lymph node positive patients or patients with microscopic positive margins. Most importantly, subset analysis did not show a benefit with gemcitabine-carboplatin chemotherapy. Among all chemotherapy-treated patients, 44% had acute grade 3 or greater treatment-related adverse events (TRAEs). This is in comparison to a 4% acute grade 3 or greater TRAEs in the surveillance patients.

Comments: Although renal function may be less optimal after nephroureterectomy, the rationale of adjuvant chemotherapy is that it would minimize overtreatment given more accurate staging with final pathology. However, many patients (estimated to be up to a third) will be ineligible for cisplatin-based adjuvant chemotherapy (GFR<50 mL/min) and subset analysis demonstrated no benefit with carboplatin-based chemotherapy. Nevertheless, this trial firmly establishes the benefit and role of adjuvant gemcitabine-cisplatin in patients with GFR>50 mL/min. This trial does not address neoadjuvant chemotherapy which conceivably would be more tolerable to patients (given better renal function with both kidneys in place) and demonstrates excellent overall survival from retrospective series. However, the risk of over-treatment of patients with neoadjuvant chemotherapy is significant given that chemotherapy is based on limited staging information obtained from ureteroscopic biopsies.

References:

1. Kleinmann N et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. Lancet Oncol. 2020 Apr published online: https://doi.org/10.1016/S1470-2045(20)30147-9.
2. Birtle A et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUTtrial): a phase 3, open-label, randomised controlled trial. Lancet. 2020 Apr 18;395(10232):1268-1277.Epub 2020 Mar 5. PMID: 32145825

CONFLICT OF INTEREST

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Renal
Honoraria: Pfizer, IPSEN
Bladder
Honoraria: Lilly
Institutional Funding: Janssen

Prostate
Honoraria: Clovis, Janssen, AstraZeneca, Sanofi, Astellas
Institutional Funding: Roche-Genentech, Bayer, Sanofi, Janssen, Medivation, Exelixis, Sanofi Genzyme

Consultant: Pfizer, Merck, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Incyte, Clovis Oncology, Medscape, UroToday

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