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Dear Readers,

In this issue, we highlight two recently published randomized trials in localized bladder cancer and a recently presented abstract on a randomized trial in metastatic urothelial cancer presented at the 2022 ESMO meeting. 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 III Multicentre Randomised Controlled Trial to Compare the Efficacy of Robotically Assisted Radical Cystectomy (RARC) and Intracorporeal Urinary Diversion With Open Radical Cystectomy (ORC) in Patients With Bladder Cancer

Clinicaltrials.gov identifier: NCT03049410

Sponsor: University College, London

Enrollment: 339

Rationale: Although robot-assisted laparoscopic radical cystectomy with extracorporeal urinary diversion has been shown to be non-inferior to open radical cystectomy, it is unknown how a totally intracorporeal or robot-assisted laparoscopic urinary diversion will affect outcomes. Therefore, this trial compares intracorporeal robot-assisted radical cystectomy with radical cystectomy in terms of recovery and days in the hospital.

Study Design: Prospective, multicenter randomized controlled trial randomizing patients undergoing radical cystectomy (1 : 1) to either intracorporeal robot-assisted radical cystectomy (iRARC) or open radical cystectomy (ORC) to assess recovery and morbidity.

Endpoints: The primary endpoint was to compare the number of days alive and out of hospital within 90 days from surgery. The secondary endpoints were numerous and included: recovery, complications, quality of life, survival, disability, stamina, activity levels, and the return to normal activities.

Results: A total of 338 patients were randomized and 306 patients ultimately underwent radical cystectomy (157 had iRARC and 149 had ORC). Most patients had an ileal conduit diversion (89%). The median number of days alive and out of the hospital within 90 days of surgery was 82 (IQR: 76-84) for patients undergoing iRARC vs. 80 (IQR: 72-83) for patients undergoing ORC (adjusted difference, 2.2 days [95% CI, 0.50-3.85]; $P = .01$). Thromboembolic and wound complications were less common with robotic surgery than open surgery. There were no statistically significant differences in cancer recurrence and overall mortality at median follow-up of 18.4 months.

Comments: There is a small statistically significant increase in days alive and out of the hospital with iRARC compared to open surgery. However, results may not be generalizable as the study was undertaken in high volume centers with surgeons with expertise in robotic surgery. In addition, the study took place during the COVID-19 pandemic and closed early so that may have affected some endpoints. It may be that in order for robotic surgery to be potentially better than open surgery, a totally intracorporeal approach may need to be employed.

Reference: JAMA. 2022;327(21):2092-2103. doi:10.1001/jama.2022.7393

Study Title: Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC)

Clinicaltrials.gov identifier: NCT03288545

Sponsor: Seagen Inc., Astellas Pharma, Merck & Co., Inc.

Enrollment: 149

Rationale: The current first-line standard of care for locally advanced or metastatic urothelial carcinoma is cisplatin-based combination chemotherapy. However, cisplatin-ineligibility limits first-line treatment options. This trial explores the efficacy of enfortumab vedotin (EV) in the first-line setting for cisplatin-ineligible patients with and without pembrolizumab as they both have shown benefit independently in the second-line and later settings. EV is an antibody-drug conjugate. It is a nectin-4-directed antibody and microtubule inhibitor conjugate.

Pembrolizumab is an anti-PD-1 monoclonal antibody approved in the treatment of urothelial cancer after chemotherapy or in platinum ineligible patients who express PDL-1.

Study Design: Cohort K of this trial included untreated cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer were randomized 1 : 1 to either EV monotherapy (1.25 mg/kg) on days 1 and 8 or in combination with pembrolizumab (200 mg) on day 1 of 3-week cycles.

Endpoints: The primary endpoint was confirmed objective response rate (ORR) per RECIST v1.1 by BICR (blinded independent central review). Secondary endpoints included duration of response (DOR) and safety (treatment-related adverse events, TRAEs). There were no formal statistical comparisons between treatment arms.

Results: A total of 149 patients, 73 in the EV arm and 76 in the combination arm, were enrolled and treated. Confirmed ORR for the EV arm was 45.2% (95%CI: 33.5-57.3) and median DOR was 13.2 months (95% CI: 6.1-16.0). Confirmed ORR for the combination arm was 64.5% (95% CI: 52.7-75.1) and median DOR was not yet reached. TRAEs occurred more commonly in the combination arm compared to the monotherapy arm and included: skin reactions (67.1% vs. 45.2%, respectively) and peripheral neuropathy (60.5% vs. 54.8%, respectively). Lesser TRAEs include ocular disorders and hyperglycemia.

Comments: There are limited options for first line therapy for cisplatin-ineligible metastatic urothelial cancer patients. This trial not only reaffirms the benefit of EV monotherapy but also demonstrates safety and efficacy with the combination of EV and pembrolizumab, that could become a new standard of care.

Reference: ESMO 2022, Late Breaking Abstract #73

Study Title: PHOTOdynamic versus white light-guided treatment of non-muscle invasive bladder cancer: randomised trial of clinical and cost-effectiveness

ISRCTN identifier: ISRCTN84013636

Sponsor: National Institute for Health and Care Research Health Technology Assessment and Newcastle upon Tyne NHS Trust

Rationale: Recurrence of non-muscle invasive bladder cancer (NMIBC) is common and the use of photodynamic diagnosis (PDD) at the time of TURBT (transurethral resection of bladder tumor) may assist in identification of tumors and may decrease recurrence of NMIBC over time. Therefore, this study aims to evaluate whether a PDD-assisted TURBT reduces the NMIBC recurrence rate compared to a standard white light (WL)-TURBT.

Study Design: Patients with NMIBC and intermediate or high risk of recurrence based on visual diagnosis were randomized (1 : 1) to PDD-TURBT or standard white light TURBT.

Endpoints: The primary endpoint was time to recurrence at 3 years of follow-up

Results: A total of 538 patients were recruited (269 patients per group), but 112 patients were excluded due to no histologic diagnosis of NMIBC or having undergone a cystectomy. After a median follow-up of 44 months, 86 of 209 (41.1%) patients in the PDD group and 84 of 217 (38.7%) patients in the white light group had recurrences. Three-year recurrence rates were 57.8% (95% CI: 50.7-64.2) and 61.6% (95% CI: 54.7-67.8) in the PDD and WL groups, respectively. There was no difference in adverse events or health-related quality of life. PDD-TURBT was 876 pounds (95% CI: -766-2518, $P = 0.591$) more costly than WL-TURBT over a 3-year follow-up period. Immediate postoperative intravesical Mitomycin C was administered in 63.2% of the PDD group and 65.9% of the WL group ($p = 0.60$).

Comments: The authors concluded that a PDD-TURBT did not reduce recurrences and was more expensive than WL-TURBT at 3 years. However, the recurrence rates appeared to clearly diverge over the first 12 months favoring PDD-TURBT. This may imply that the benefit of a single PDD-TURBT may only last for 12 months. Finally, the trial was designed to detect 214 recurrences but only 170 patients recurred so a smaller, clinically significant difference may exist but was not identified because so many patients were excluded from the analysis.

Reference: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200092

DISCLOSURES:

Cora N. Sternberg

Consultant: Pfizer, Merck Ga, MSD, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Immunomedics now Gilead, Amgen, Clovis Oncology, Bayer, Bristol Myers Squibb, Seattle Genetics, Impact Therapeutics, Foundation Medicine, UroToday, Medscape

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