Editorial

Round Up

PHASE I TRIAL OF INTRAVESICAL BACILLUS CALMETTE–GUERIN COMBINED WITH INTRAVENOUS PEMBROLIZUMAB IN RECURRENT OR PERSISTENT HIGH-GRADE NONMUSCLE-INVASIVE BLADDER CANCER AFTER PREVIOUS BACILLUS CALMETTE–GUÉRIN TREATMENT

This is the first Phase I trial of intravesical Bacillus Calmette–Guerin (BCG) in combination with systemic pembrolizumab in patients with high-grade nonmuscle-invasive bladder cancer (HGNMIBC) who had persistent or recurrent disease after prior intravesical therapy with BCG.[1] The primary objective was the safety and the secondary objective was to determine the no evidence of disease (NED) rate using cystoscopy and cytology at 3 months following BCG treatment. Eighteen patients were included in the study. Six doses of 200 mg pembrolizumab were administered every 3 weeks over 16 weeks concurrently with 6 weekly doses of BCG (50 mg TICE) beginning at week 7 (Day 1 of cycle 3). Adverse events (AEs) were 49 Grade 1, 30 Grade 2 (88% of AEs), and 1 Grade 4 (adrenal insufficiency). Eleven patients finished the treatment, and two patients died during the study. Of the 13 patients treated, 9 (69%) patients had NED at 3 months following BCG treatment. This study found that combining BCG and pembrolizumab in treating HGNMIBC is safe allowing complete treatment of most patients.

STEREOTACTIC ABLATIVE BODY RADIOTHERAPY FOR PRIMARY KIDNEY CANCER

Stereotactic ablative body radiotherapy (SABR) is a novel noninvasive alternative for patients with primary renal cell cancer who do not undergo surgical resection. The FASTRACK II clinical trial was an international, nonrandomized, Phase 2 study on the efficacy of SABR.[2] Patients aged >18 years, who had biopsy-confirmed primary renal cell cancer, only a single lesion, medically inoperable, were at high risk of complications from surgery, or declined surgery and had an Eastern Cooperative Oncology Group (ECOG) Performance Status (ECOG) score of 0–2, were included in the study. Patients received either a single fraction (n = 23) SABR of 26 Gy for tumors 4 cm or less or 42 Gy in three fractions (n = 47) for tumors more than 4–10 cm in maximum diameter. The primary end point was local control, defined as no progression of the primary renal cell cancer, as evaluated by the RECIST criteria (version 1.1). From July 2016 to February 2020, 70 patients were enrolled. The median tumor size was 4 · 6 cm (interquartile range [IQR 3 · 7–5 · 5]). All patients had T1 – T2a and N0 – N1 disease. The median follow-up was 43 months (IQR 38–60). Local control at 12 months was 100% (P < 0·0001). Seven (10%) patients had Grade 3 treatment-related AEs with no treatment-related or cancer-related deaths. SABR was found to be an effective treatment with no observed local failures or cancer-related deaths with an acceptable side effect profile and renal function after SABR.

ADMINISTERING [^{177}LU] LU-PSMA-617 BEFORE RADICAL PROSTATECTOMY IN MEN WITH HIGH-RISK LOCALIZED PROSTATE CANCER (LUTECTOMY): A SINGLE-CENTER, SINGLE-ARM, PHASE 1/2 STUDY

Eapen *et al*.[3] investigated upfront Lu-PSMA-617 in men with high-risk localized prostate cancer (HRCaP) Prostate Specific Antigen (PSA) >20 ng/mL, International Society of Urological Pathology Grade Group (ISUP GG) 3–5, and cT2c), with high tumor uptake on 68Ga-PSMA positron emission tomography/computed tomography before robotic radical prostatectomy. Cohort A (n = 10) received one cycle and cohort B (n = 10) received two cycles of Lu-PSMA-617 (5 GBq) followed by surgery 6 weeks later. The primary endpoint was tumor radiation-absorbed dose. From May 2020 to April 2022, 20 patients were enrolled. The median PSA was 18 ng/mL (interquartile range [IQR] 11–35), 18 (90%) had GG >3, and six (30%) had N1 disease. The median (IQR) highest tumor radiation-absorbed dose after Cycle 1 for all lesions was 35.5 Gy (19.5–50.1), with 19.6 Gy (11.3–48.4) delivered to the prostate. Five patients received radiation to lymph nodes. Nine (45%) patients achieved >50% PSA decline. The most common AEs related to [^{177}Lu] Lu-PSMA-617 were Grade 1 fatigue in eight (40%), nausea in seven (35%), dry mouth in six (30%), and thrombocytopenia in four (20%) patients. No Grade 3/4 toxicities or Clavien 3–5 complications occurred. The authors concluded that up to two cycles of Lu-PSMA-617 given before surgery in men with HRCaP are safe and effective, delivering targeted doses of radiation to sites of tumors with high PSMA expression. It was well tolerated with minimal effect on surrounding tissues, making surgery after treatment safe and feasible. Promising imaging, biochemical, and pathological responses were seen.

OFFICE-BASED TRANSPERINEAL BIOPSY IS TOLERABLE, DOES NOT COMPROMISE CANCER DETECTION, AND DOES NOT RESULT IN INFECTIOUS COMPLICATIONS

This multicentric, randomized trial[4] compared the infectious complications of transperineal biopsy without

antibiotic prophylaxis versus transrectal biopsy with targeted prophylaxis (rectal culture for fluoroquinolone-resistant bacteria and antibiotic targeting to culture and sensitivity) under local anesthesia in biopsy-naive patients. The primary outcome was postbiopsy infection detected by a prospective medical review and patient-reported outcomes on a 7-day survey. The secondary outcomes included cancer detection, noninfectious complications, and a Numerical Rating Scale (0–10) for biopsy-related pain and discomfort during and 7 days after biopsy. After randomization, transperineal ($n = 328$) and transrectal ($n = 330$) biopsies were performed. There were no infections in the transperineal biopsy arm compared with 4 (1.4%) infections in the transrectal biopsy arm. The rates of other complications were very low and similar. Importantly, the detection of clinically significant cancer was similar (53% transperineal vs. 50% transrectal). Participants in the transperineal arm experienced worse periprocedural pain (0.6 adjusted difference [0–10 Scale], 95% confidence interval [CI] 0.2, 0.9), but the effect was small and resolved by 7 days. The authors concluded that office-based transperineal biopsy is tolerable, does not compromise cancer detection, and does not result in infectious complications. Transrectal biopsy with targeted prophylaxis achieved similar infection rates. The absence of infectious complications with transperineal biopsy without the use of preventative antibiotics is noteworthy.

ENFORTUMAB VEDOTIN AND PEMBROLIZUMAB IN UNTREATED ADVANCED UROTHELIAL CANCER

This was a Phase 3, global, open-label, randomized trial to compare the efficacy and safety of enfortumab vedotin and pembrolizumab (EVP) versus platinum-based chemotherapy (PCT) in patients with previously untreated locally advanced or metastatic urothelial carcinoma (ULA/mUC).[5] Patients were randomly assigned in a 1:1 ratio to receive 3-week cycles of enfortumab vedotin (on Days 1 and 8) and pembrolizumab (on Day 1) (EVP group) or gemcitabine and either cisplatin or carboplatin (PCT group). The primary end points were progression-free survival (PFS) as assessed by blinded independent central review and overall survival (OS).

After randomization, 442 received EVP, and 444 received PCT. The median duration of follow-up for survival was 17.2 months. PFS was longer in the EVP group than in the chemotherapy group (median, 12.5 months vs. 6.3 months; hazard ratio [HR] for disease progression or death, 0.45; 95% CI, 0.38–0.54; $P < 0.001$), as was OS (median, 31.5 months vs. 16.1 months; HR for death, 0.47; 95% CI, 0.38–0.58; $P < 0.001$). The median number of cycles was 12 (range, 1–46) in the enfortumab vedotin–pembrolizumab group and 6 (range, 1–6) in the chemotherapy group. Treatment-related AEs of Grade 3 or higher occurred in 55.9% of the patients in the EVP group and 69.5% of those in the chemotherapy group. The authors concluded that the use of EVP resulted in significantly better outcomes than chemotherapy in patients with ULA/mUC, with a consistent safety profile.

CAN NERVE MONITORING DURING RADICAL PROSTATECTOMY IMPROVE FUNCTIONAL OUTCOMES? A RANDOMIZED TRIAL

The study investigated the impact of using the ProPep Nerve Monitoring System during robot-assisted radical prostatectomy (RARP) on postoperative functional outcomes, particularly pudendal nerve sparing, in 100 patients undergoing unilateral nerve-sparing or nonnerve-sparing RARP.[6] Men were randomized to receive either ProPep nerve monitoring during surgery or standard RARP without monitoring, respectively.

Functional outcomes were assessed at 3, 6, and 12 months postoperatively. Results showed no significant difference in the mean International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form(ICIQ-SF) scores between the intervention and control groups at 12 months. Secondary outcomes and continence rates did not significantly differ between groups, although the intervention group showed a slightly higher continence rate at 6 months.

Overall, intraoperative nerve monitoring with ProPep did not lead to improved functional outcomes post-RARP. Larger studies are suggested to explore whether ProPep monitoring may reduce the time to continence after RARP.

INFLUENCE OF LAMINA PROPRIA INVASION EXTENSION ON T1 HIGH-GRADE NONMUSCLE-INVASIVE BLADDER CANCER

The study[7] aimed to assess the prognostic significance of T1 substaging in patients with nonmuscle-invasive bladder cancer treated with either BCG therapy or immediate radical cystectomy (iRC). The retrospective study analyzed 411 T1 high-grade NMIBC patients treated between 2000 and 2020, focusing on lamina propria invasion characteristics extracted from pathology reports. OS, cancer-specific survival (CSS), and metastasis-free survival (MFS) were calculated using the Kaplan–Meier method. Patients with extensive/multifocal (E/M) LP invasion were more likely to undergo iRC. E/M LP invasion was associated with poorer MFS and CSS in the BCG cohort. Among BCG-treated patients, E/M LP invasion independently correlated with progression. However, T1 substaging was not linked to upstaging at iRC. The findings underscore the prognostic value of T1 substaging, particularly in predicting outcomes following BCG treatment, advocating for its inclusion in pathology reports. This study emphasizes the importance of individualized treatment strategies based on T1 substaging in NMIBC patients.

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