Year in Review 2018 by LACOG Genitourinary Cancer Group: Urological Tumors

Revisão do ano 2018 pelo grupo de cancer genitourinário do LACOG: Tumores Urológicos

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ABSTRACT

Several and important changes in the treatment of urological tumors occurred in 2018. The studies with apalutamide (SPARTAN) and enzalutamide (PROSPER) prior to the development of metastases benefited patients with castration resistant prostate cancer. Prostate radiotherapy to the metastatic prostate cancer improves overall survival (OS) in men with new diagnosed and with low metastatic disease burden per CHARTEED criteria. In another analysis of this trial, the abiraterone improve OS even in low-risk de novo M1 castration-sensitive prostate cancer. A phase III trial (CARMENA) assessed the utility of cytoreductive nephrectomy in conjunction with TKI’s and concluded that we could not offer it in intermediate and poor-risk patients of renal cell carcinoma (RCC). Combined immunotherapy with nivolumab plus ipilimumab (CHECKMATE-214) resulted in a greater objective response rate and prolonged OS in intermediate- and poor-risk patients with metastatic RCC. And in upper tract urothelial cancer, a study showed that adjuvant chemotherapy given after nephroureterectomy improves OS (POUT).

Keywords: Review Literature as Topic; Urologic Neoplasms; Prostatic Neoplasms; Urinary Bladder Neoplasms; Kidney Neoplasms

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Financial support: none to declare.
Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.

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Received on: December 13, 2018 | Accepted on: March 17, 2019
DOI: 10.5935/1806-6054.20190003
Several and important changes in the treatment of urological tumors occurred in this year. Until this time, there have been no drugs proven to benefit men with non-metastatic prostate cancer that has progressed despite standard hormonal therapy. The studies with apalutamide (SPARTAN) and enzalutamide (PROSPER) prior to the development of metastases clearly broke a paradigm, benefiting patients whose prostate cancer no longer responded to conventional hormonal therapy. Prostate radiotherapy to the metastatic prostate cancer improves overall survival, but only in men newly diagnosed who have a low metastatic disease burden per CHARTEED criteria (the latest arm to report from the STAMPEDE trial). Another analysis of this multi arm trial, the abiraterone improve overall survival (OS) even in low-risk de novo M1 castration-sensitive prostate cancer (CSPC) independently of risk criteria (LATITUDE or CHARTEED). Cytoreductive nephrectomy (CN), essentially debulking of the primary tumor in the setting of metastatic renal cell carcinoma (mRCC), has been a mainstay of therapy for decades. In this year, however, a phase III trial (CARMENA) assessed the utility of CN in conjunction with TKI’s and concluded that we could not offer it in intermediate and poor-risk patients of renal cell carcinoma. The success of immunotherapy in the second line kidney cancer brought the combination to test in the first-line treatment scenario. Combined immunotherapy with nivolumab plus ipilimumab (CHECKMATE-214) resulted in a greater objective response rate (ORR) and prolonged overall survival (OS) compared to sunitinib in intermediate and poor-risk patients with previously untreated advanced or metastatic renal cell carcinoma (RCC). Moreover, in upper tract urothelial cancer, we finally had a study in this specific population, showing that adjuvant chemotherapy given after nephroureterectomy improves survival significantly (POUT).

SPARTAN¹ and PROSPER²: The phase III SPARTAN randomized 1207 men with nonmetastatic castration-resistant prostate cancer (CRPC) and a prostate-specific antigen (PSA) doubling time of 10 months or less. Patients were randomized, in a 2:1 ratio, to receive apalutamide or placebo in concomitance with androgen-deprivation therapy (ADT). Median metastasis-free survival was 40.5 months in the apalutamide group versus (vs) 16.2 months in the placebo group (hazard ratio [HR] for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; P < 0.001). Time to progression with symptoms was longer with apalutamide than with placebo (HR 0.45; 95% CI, 0.32 to 0.63; P < 0.001). Most common adverse events were rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%). This study found strong evidence of apalutamide benefit in metastasis-free survival and time to symptomatic progression among men with non-metastatic castration-resistant prostate cancer. In a similar scenario (M0 CRPC, PSA doubling time ≤ 10 months and PSA ≥ 2 ng/mL), the phase III PROSPER randomized, in a 2:1 ratio, 1401 patients to enzalutamide 160mg or placebo in concomitance with androgen-deprivation therapy. Enzalutamide significantly prolonged median metastasis-free survival (36.6 months vs 14.7 months [P < 0.0001]) and time to PSA progression (37.2 months vs 3.9 months [P < 0.0001]) compared to placebo. Toxicities were greater in the group enzalutamide (any grade: 87% vs 77%). The most common adverse event in patients receiving enzalutamide was fatigue. Adverse events of special interest that occurred more frequently
in the enzalutamide group than the placebo group were hypertension (in 12% vs. 5%), major adverse cardiovascular events (in 5% vs. 3%), and mental impairment disorders (in 5% vs. 2%).

**STAMPEDE**

The STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial is a multi-stage, multi-arm study that has enrolled since 2005 over 10,000 patients with localized and biochemical recurrence high-risk patients and advanced prostate cancer. In this study, each experimental arm is compared with the standard arm, which can be modified over time with new data demonstrating OS for this population. In 2007, the STAMPEDE and LATITUDE trials demonstrated a clinically meaningful benefit in OS and other important endpoints with abiraterone plus prednisone plus ADT for CSPC. Importantly, although the STAMPEDE study demonstrated OS improvement with abiraterone in all patients with metastatic disease (M1), the LATITUDE study only enrolled patients with metastatic high-risk disease, defined by 2 of the 3 following criteria: ≥ 3 bone lesions, Gleason ≥ 8 and visceral metastasis. STAMPEDE abiraterone comparison data was presented with stratification by disease risk and volume at the 2018 European Society of Medical Oncology (ESMO) congress. That analysis included 428 low-risk and 473 high-risk metastatic patients and in both groups demonstrated OS benefits with the addition of abiraterone and prednisone to ADT, with an absolute improvement in OS of 4.4% and 19.7%, respectively. Based on this data, abiraterone and prednisone should be considered in patients with de novo M1 CSPC, regardless of the disease risk.

Another important data from the STAMPEDE trial was the comparison of the standard of care (SOC) arm (ADT ± docetaxel) versus SOC plus radiation therapy (RT) for the prostate in patients with de novo M1 CSPC. This analysis included 2,061 patients and demonstrated that RT improved failure-free survival but not OS in the overall population. However, in a pre-planned subgroup analysis, patients with low volume (CHARTTEED criteria) disease demonstrated an OS improvement with RT plus SOC (3 year-OS of 81% versus 71%. HR: 0.68). These results are further corroborated by the HORRAD trial, which also evaluated the benefit of RT for the prostate in M1 CSPC and did not demonstrate an OS benefit in an unselected population, but suggested benefit of RT in patients with less than five bone metastasis in a post-hoc analysis. Therefore, based on these data, RT for the prostate should be discussed for patients with CSPC and low metastatic burden.

**CARMENA**

The first references of nephrectomy in metastatic renal tumor pointed to an important benefit of surgery followed by immunotherapy (interferon) versus isolated systemic treatment. However, after approvals of potent tyrosine kinase inhibitors, robust data involving nephrectomy in this setting have become essential. The phase 3 study, CARMENA trial, presented at ASCO 2018 and recently published, attempted to demonstrate the use of sunitinib alone is not inferior to the surgical treatment followed by sunitinib in patients with metastatic renal cancer. It is important to note that patients with an ECOG 1 performance corresponded to more than 40% of the study population and only subjects with intermediate or unfavorable risk were included. With a median follow-up of 50.9 months, in the evaluation of the entire study population, the arm that used sunitinib alone was not inferior in overall survival, at 18.4 months versus 13.9 months. At this planned interim analysis, the upper boundary of the 95% confidence interval for the hazard ratio did not exceed the fixed non inferiority limit. Thus, sunitinib alone was not inferior to nephrectomy followed by sunitinib. It seems clear the lack of benefit of nephrectomy in patients with advanced disease with unfavorable risk and with potential use of target therapy. However, little is known about surgery in patients with more favorable risks or even with the use of the new checkpoint inhibitors.

**Checkmate-214**

The treatment of mRCC patients has been through significant changes in the past few years. Nivolumab was initially approved for patients with clear-cell mRCC in the second line after failure of first line VEGFR (Vascular Endothelial Growth Factor Receptor) TKI (Tyrosine Kinase Inhibitors). The Checkmate 214 trial was designed to compare in the intermediate and poor risk patients, using IMDC criteria, the efficacy of immunotherapy combination with ipilimumab and nivolumab against the standard of care with sunitinib in clear-cell mRCC in the first line setting. A total of 1096 patients were randomized to receive sunitinib or ipilimumab plus nivolumab for 4 cycles followed by nivolumab. After a median follow-up of 25.2 months, patients with intermediate and poor-risk disease treated with ipilimumab plus nivolumab had a significant improvement in OS compared to sunitinib, with 37% reduction in the risk of death (HR 0.63; p < 0.001). There was also a significant increase in the ORR from 27% to 42% (p < 0.001) for sunitinib and ipilimumab plus nivolumab, respectively. Of note, the complete response (CR) rate was 9% compared to only 1% for the immunotherapy combination and sunitinib, respectively. Median progression free survival (PFS) difference and 8.4 months, respectively for ipilimumab plus nivolumab (and sunitinib) failed to achieve statistical significance (HR 0.82; p = 0.03) according to the pre-specified boundaries. ITT analysis (including all risk groups) also showed an improvement of OS in benefit of ipilimumab + nivolumab. However, when evaluating the good-risk population alone (exploratory endpoint), patients treated with the immunotherapy combination had a worse median PFS and worse ORR, although the OS analysis is still premature in this population. Of note, it is important to point out that the CR rate of the good-risk population was higher than sunitinib (11% versus 6%, respectively). It was observed that patients with high PD-L1 expression had higher ORR, but it is important to point out that even for the PD-L1 negative intermediate and poor-risk patient population the OS analysis was in
favor of immunotherapy combination. The adverse events profile was distinct between both treatment groups due to the different mechanism of action. The adverse events of special interest (immune mediated) for the immunotherapy combination were colitis (5%), hepatitis (6%), adrenal insufficiency (3%), hypophysitis (3%) and skin rash (3%). The incidence of all-grade adverse events were similar in treatment groups (93% and 97%), but the treatment discontinuation rate was higher for patients treated with ipilimumab plus nivolumab (22% versus 12%).

**POUT**

The POUT trial was the first prospective, phase III, to evaluate the role of adjuvant platinum-based chemotherapy after the resection of upper tract urothelial carcinoma. Despite the fact that the trial was terminated early because of efficacy favouring the chemotherapy arm, the combination of gencitabine and cisplatin or carboplatin showed a significant improvement in disease-free survival at two years: 51% for surveillance (95% CI: 39, 61) and 70% for chemotherapy (95% CI: 58, 79), with a HR = 0.47 (95% CI: 0.29, 0.74) in favour of chemotherapy (P = 0.0009). A trend of benefit of overall survival was also presented, but the data were immature for this endpoint. Thus, the adjuvant platinum based chemotherapy should be considered a new standard of care in these patients.8

**REFERENCES**


