

Immune checkpoint inhibitors in penile cancer

Carlo Buonerba^{*1}, Luca Scafuri^{1,2}, Ferdinando Costabile^{1,2}, Bruno D'Ambrosio², Simona Gatani², Pasquale Verolino³, Rossella Di Trolio⁴, Vincenzo Cosimato⁵, Antonio Verde¹ & Giuseppe Di Lorenzo²

¹Centro di Referenza Nazionale per l'Analisi e Studio di Correlazione tra Ambiente, Animale e Uomo, Istituto Zooprofilattico Sperimentale del Mezzogiorno, Portici 80055, Italy

²Oncology Unit, Hospital 'Andrea Tortora', ASL Salerno, Pagani, Italy

³Multidisciplinary Department of Medical-Surgical & Dental Specialties, Plastic Surgery Unit, University of Campania Luigi Vanvitelli, Naples, Italy

⁴Unit of Melanoma, Cancer Immunotherapy & Development Therapeutics, Istituto Nazionale Tumori Istituto di Ricovero e Cura a Carattere Scientifico Fondazione G. Pascale, Naples, Italy

⁵Division of Laboratory Medicine, Civil Hospital 'Maria SS. Addolorata', ASL Salerno, Eboli, Italy

⁶Department of Medicine & Health Sciences 'Vincenzo Tiberio', University of Molise, Campobasso, Italy

*Author for correspondence: carlo.buonerba@unina.it

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First draft submitted: 1 April 2021; Accepted for publication: 14 April 2021; Published online: 21 May 2021

Keywords: immune checkpoint inhibitors • immunotherapy • penile cancer

Penile cancer (PCa) is a rare yet deadly disease, with an incidence rate varying in the range of 1–10 cases per 100,000 men across countries worldwide and a 5-year survival rate ranging from 90% in stage I patients to a dismal 5% in stage IV patients [1]. With 300 men dying annually of advanced/recurrent PCa in the USA alone [2], effective systemic therapeutic options remain a highly unmet need, and only a few currently available chemotherapy agents are recommended on the basis of noncomparative prospective [3,4] or retrospective [5] studies. The EGFR may represent a valuable druggable target, based on the frequent expression of EGFR in PCa [6–8] and preliminary evidence of efficacy obtained with anti-EGFR agents [9], although more supporting prospective data are needed for approval and its widespread use in clinical practice.

The advent of immune check-point inhibitors (ICI), mainly directed at programmed death-1 (PD-1), programmed death ligand-1 (PDL-1) or cytotoxic t-lymphocyte antigen 4 (CTLA-4), has truly revolutionized therapy of solid malignancies and may also expand the limited treatment landscape of advanced PCa. In fact, PD-L1 expression, a known marker predictive of efficacy of anti-PD-1/PDL-1 inhibitors across different solid tumors [10], was reported in 51% of cases in a surgical cohort of 35 men with PCa undergoing penectomy, and in 69% of those with node-positive disease [11]. In another retrospective analysis of 53 archival PCa specimens, 40% of cases were positive for PDL-1, with 38% of node-positive tumors showing PD-L1 expression [12]. As a result of the biological rationale and the compelling need for additional systemic options, a few ICIs have been explored in patients with advanced PCa, with promising results. Chahoud [13] and others originally reported on two cases who received anti-PD-1 agent pembrolizumab after chemotherapy, radiation and surgery: one man with a high tumor mutation burden achieved a complete response maintained for >38 months and another man achieved a partial response, maintained for >18 months. Conversely, a report of a Phase II trial conducted in various rare malignancies showed that pembrolizumab was not capable of providing any benefits in two patients with microsatellite-stable PCa, while a durable response was obtained in a single man with a microsatellite instability high tumor [14]. Combination of anti-CTLA-4 agent ipilimumab and anti-PD-1 agent nivolumab administered at standard doses was associated with a prominent response in a patient refractory to paclitaxel, ifosfamide and cisplatin who was selected for treatment with ICIs on the grounds of the results of extensive molecular analysis showing high PDL-1

expression, microsatellite instability and tumor mutational burden, as well as alterations in DNA mismatch repair genes [15]. Conversely, in a single-arm, multicohort, Phase II trial, assessing nivolumab and ipilimumab in patients with advanced rare genitourinary cancers not selected on the grounds of any molecular biomarker, only two of five patients evaluable for radiological response showed stable disease [16]. Finally, anti-PD-1 agent cemiplimab tested in patients with advanced squamous cell carcinoma of the skin was associated with a partial response in a single patient with metastatic PCa included in the trial [17], and a complete response was reported in a separate case report of an HIV+ patient receiving cemiplimab [18].

Overall, the scanty data reported suggest that some, albeit unsatisfactory progress has been made over the past 5 years in the field of immunotherapy of PCa [19]. One unexplored, yet potentially effective strategy is the use of combination therapy based on ICIs plus chemotherapy or biological agents. One meta-analysis including quantitative data from 5388 patients with different solid tumors showed that ICI plus chemotherapy was associated with a significantly higher tumor response rate (relative risk: 2.51; 95% CI: 1.82–3.47), decreased chances of progression (hazard ratio [HR]: 0.62; 95% CI: 0.53–0.74), and death (HR: 0.69; 95% CI: 0.61–0.78), compared with single agent ICI or chemotherapy [20]. Considering that anti-PD-1 agents such as pembrolizumab have been successfully combined with cisplatin and fluorouracil [21], combination of cisplatin + 5-fluorouracil, which has proven to be active as a first-line therapy of advanced PCa [5], with pembrolizumab appears to be an appealing experimental therapeutic option. Conversely, in patients who are unfit for chemotherapy, but are candidates for anti-EGFR therapy on the basis of molecular data, combination of an anti-PD-1 agent like nivolumab and an anti-EGFR agent like cetuximab has proven to be well tolerated [22] and may also represent a promising therapeutic option. Finally, with the hurdles associated with the rarity of the disease, which makes it difficult for pharmaceutical companies to obtain regulatory approval, patient selection for ICIs based on known predictive markers, including microsatellite instability, tumor mutational burden, PDL-1 expression, will be mandatory before treatment with an ICI, especially as these biomarkers become more widely available in clinical practice. The rarity of this disease, as in the case of other rare tumors, makes it more difficult to draw an exact line between an experimental and a nonexperimental setting even in common clinical practice. An international effort made by independent scientists, governmental institutions and pharmaceutical companies is compelling in order to increase funding to support research against such a deadly and neglected disease; provide access to nonapproved, high-cost novel agents based on a sound scientific rationale; and increase data sharing among clinicians and researchers through the use of web-based public repositories, specifically designed to collect data on rare diseases. These goals can be better achieved if both patients and clinicians are aware that PCa, as a rare disease, must be treated at referral centers with proven expertise.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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