Safety and efficacy of immunotherapy in the treatment of genitourinary tract tumors

Peltzman, Ador

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Ador Peltzman

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Abbreviations

1. OS- Overall Survival
2. UTI- Urinary Tract Infection
3. CT- Computed Tomography
4. US- Ultrasound
5. CAD- Coronary Artery Disease
6. COPD- Chronic Obstructive Pulmonary Disease
7. TURBT- Transurethral Resection of Bladder Tumors
8. NMIBC- non-muscle-invasive Bladder Cancer
9. PFS- Progression-Free Survival
10. RFS- Recurrence-Free Survival
11. BCG- Bacillus Calmette-Guerin
12. UC- Urothelial Carcinoma
13. FDA- Food and Drug Administration
14. PD-1- Programmed cell death protein 1
15. PD-L1- Programmed cell death Ligand 1
16. ORR- Overall Response Rate
17. AE- Adverse Events
18. UTUC- Upper Tract Urothelial Carcinoma
19. RCC- Renal Cell Carcinoma
20. ccRCC- clear cell Renal Cell Carcinoma
21. PFS- Progression-Free Survival
22. TKI- Tyrosine Kinase Inhibitors
23. CRR- Complete Response Rate
24. IMDC- International Metastatic RCC Database Consortium
25. LAG3- Lymphocyte-Associated Gene 3

26. MHCII- Major Histocompatibility Complex Class II

27. TNFα- Tumour Necrosis Factor Alpha

28. INFγ- Interferon Gamma

29. VISTA- V-Domain Immunoglobulin Suppressor of T cell Activation

30. APC- Antigen Presenting Cells

31. MDSC- Myeloid-Derived Suppressive Cells

32. ICOS- Inducible co-stimulator

33. PI3K- Phosphoinositide 3-Kinase

34. 1b- based on one randomized controlled phase 3 trial

35. TMB- Tumour Mutational Burden

36. MCP- Microenvironment Cell Population

37. CTC- Circulating Tumour Cells

38. EpCAM- Epithelial Cell Adhesion Molecule

39. ADT- Androgen Deprivation Therapy

40. mCRPC- metastatic Castration-Resistant Prostate Cancer

41. mHSPC- metastatic Hormone-Sensitive Prostate Cancer

42. PAP- Prostatic Acid Phosphatase

43. TAA- Tumor-Associated Antigens

44. hTERT- human Telomerase Reverse Transcriptase

45. GM-CSF- Granulocyte-Macrophage Colony-Stimulating Factor

46. PBMCs- Peripheral Blood Mononuclear Cells

47. dMMR- deficient Mismatch Repair

48. TCR ζ- T-cell receptor zeta

49. AR LBD- Androgen Receptor Ligand-Binding Domain

50. VEGF- Vascular Endothelial Growth Factor

51. TGCTs- Testicular germ cell tumors

52. TRT- Targeted Radionuclide Therapy

53. HRD- Homologous Recombination Deficiency

54. CTAg- Cancer/Testis Antigens

55. ICs- Infiltrating Immune Cells

56. TCs- Tumor Cells

57. FIHC- Fluorescence Immunohistochemistry

58. BV- Brentuximab-Vedotin

59. TIM-3- T-cell Immunoglobulin and Mucin domain-3

60. HNPCC- Hereditary Nonpolyposis Colorectal Carcinoma

61. PPV- Positive Predictive Value

62. IVR- Intravesical Recurrence

63. RNU- Radical Nephroureterectomy

64. FGFR- Fibroblast Growth Factor Receptor

65. NAC- Neo Adjuvant Chemotherapy

66. MIS- Minimally Invasive

67. DFS- Disease-Free Survival

68. MFS- Metastasis Free Survival

69. CPS- Combined Positive Score

Contents

1. Abstract

Genitourinary tract tumors are found in the urinary system and the male reproductive system. These tumors can occur anywhere along the urinary tract, including the bladder, kidney, prostate, ureters, and testicles. Urothelial carcinoma (UC), also known as transitional cell carcinoma, accounts for 95% of bladder cancers and 10% of all primary renal cancers.

Chemotherapy remains the primary treatment for urothelial carcinoma, but progression-free survival (PFS) and overall survival (OS) are short. In addition, the recurrence rate is high, and many patients are not eligible for chemotherapy due to adverse events and comorbidities.

Immunotherapy and immune checkpoint inhibitors (ICIs) in particular have gained popularity in recent years in the management of many types of cancers. Certain cancers utilize upregulation of immune checkpoints, which leads to inhibition of immune cell activation, and allows the cancer cells to evade immune surveillance. ICIs block the immune checkpoint proteins (such as CTLA4, PD-1, and PD-L1), thus restoring the immune system's function against the cancer cells.

Multiple ongoing clinical trials are currently evaluating the safety and efficacy of ICIs and new combination therapies in treating patients with advanced malignancies compared to standard chemotherapy.

This review is a compilation of the latest information based on results from multiple clinical trials about the safety and effectiveness of immunotherapy used in major urogenital tumors (bladder cancer, kidney cancer, prostate cancer, testis cancer, upper urinary tract cancer).

Keywords: genitourinary tract tumors, immunotherapy, immune checkpoint inhibitors, clinical trials

2. Sažetak

Tumori genitourinarnog trakta su tumori urinarnog sustava te muških reproduktivnih organa. Ovi tumor mogu nastati na bilo mjestu u urinarnom traktu, uključujući mokraćni mjehur, bubrege, prostatu, uretere i testise. Urotelijalni karcinom (UC), poznat i pod nazivom karcinom prijelaznog epitela, čini 95% svih karcinoma mokraćnog mjehura i do 10% svih primarnih karcinoma bubrega.

Kemoterapija ostaje primarna vrsta liječenja urotelnih karcinoma, no preživljenje bez progresije bolesti (progression free survival -PFS) te ukupno preživljenje (overall survival – OS) su kratki. Dodatno, postotak relapse je visok, a mnogi pacijenti nisu dobri kandidati za kemoterapiju zbog komorbiditeta ili nuspojava.

Imunoterapija i primjena inhibitora kontrolnih točaka zadnjih godina dobivaju na značaju u terapiji mnogih vrsta tumora. Neke vrste tumora moduliraju imuni sustav uzrokujući inhibiciju aktivacije imunih stanica, te stanice tumora na taj način izbjegavaju reakciju imunog sustava. Inhibitori kontrolnih točaka blokiraju imunoregulatorne proteine (poput CTLA4, PD-1 i PD-L1), te na taj način iznova omogućuju reaktivnost imunog sustava prema tumorskim stanicama.

Brojna klinička istraživanja trenutno evaluiraju sigurnost i učinkovitost inhibitora kontrolnih točaka u monoterapiji ili u kombinaciji s drugim lijekovima u liječenju pacijenata s uznapredovalim malignim bolestima u usporedbi s klasičnom kemoterapijom.

Ovaj pregledni diplomski rad obrađuje najnovije rezultate kliničkih istraživanja u pogledu sigurnosti i učinkovitosti imunoterapije u liječenju glavnih tipova urogenitalnih tumora (karcinom mokraćnog mjehura, karcinom bubrega, karcinom prostate, karcinom testisa, karcinomi proksimalnog dijela urinarnog trakta).

Ključne riječi: tumori genitourinarnog trakta, imunoterapija, inhibitori kontrolnih točaka, klinička istraživanja.

3. Introduction

Genitourinary tract tumors can occur anywhere along the urinary tract and the male reproductive system, including the bladder, kidney, ureters, prostate, and testes. Bladder cancer is the most common malignancy involving the urinary system, and it is the 9th most common cancer in the world, accounting for 3% of global cancer diagnoses [1]. It is estimated that each year in the US, more than 80,000 new cases of bladder cancer are diagnosed, and 17,000 deaths are attributed to bladder cancer. Urothelial cancer (UC) is the most common form of bladder cancer, and it accounts for more than 95% of all reported cases. However, UC can also arise in other areas that are lined by urothelium, such as the ureters, urethra, renal pelvis and calyces. The median 5-year survival rate in the US for patients with early non-metastatic disease is 77%, however, 30% of patients present with muscle-invasive bladder cancer (MIBC), and in that case the 5-year survival drops to 5% [2].

Radical cystectomy plus neoadjuvant or adjuvant platinum-based chemotherapy are the commonly methods of care for MIBC patients. Although platinum-based chemotherapy is used to control metastatic UC, progression occurs quickly due to the development of chemotherapy resistance. Immune checkpoint inhibitors (ICIs), a type of novel immunotherapy, have gained acceptance in the past several years and have been found to enhance outcomes in patients with metastatic urothelial carcinoma. The FDA approved the use of ICIs as first-line treatment of metastatic urothelial carcinoma in patients who are unsuitable for cisplatin chemotherapy and have tumors that express PD-L1 based on findings from the KEYNOTE-052 and IMvigor 210 studies [3].

Pembrolizumab is an ICI that targets the PD-1 receptor. Based on the results of the KEYNOTE-045 phase III clinical trial, the FDA authorized it’s us as a second-line treatment for patients with metastatic UC. Pembrolizumab had shown to increase the OS, and it has a good safety profile in patients with recurrent disease. Avelumab is an ICI that targets PD-L1, which was also approved as second-line care for metastatic UC. Avelumab was tested as a maintenance treatment in patients with malignant UC in the JAVELIN bladder trial, and it was reported to significantly improve the OS in

PD-L1 positive patients [2]. Other ICIs that are approved as second-line therapy include atezolizumab, nivolumab, and durvalumab.

4. Urothelial Carcinoma of the Bladder

Bladder cancer is currently the sixth most frequent cancer in the United States, and the ninth most common cancer in the world [1]. Most cases are diagnosed after the development of symptoms such as hematuria and dysuria. Twenty percent of symptomatic patients will have locally progressive or metastatic cancer [4]. Other symptoms that might present include polyuria, pelvic pain, UTIs, and weight loss [5]. Widespread screening for bladder cancer is not recommended even in high-risk groups due to high costs, lack of specificity, and over detection rates. Smoking is the most common cause of bladder cancer [6]. "Former smokers (119.8 per 100,000 person-years; HR, 2.22; 2.03– 2.44) and current smokers (177.3 per 100,000 person-years; HR, 4.06; 3.66–4.50) had higher risks of bladder cancer than never-smokers (39.8 per 100,000 person-years)" [7]. The majority of patients with bladder cancer are over 70 years old and have other co-morbidities such as diabetes, hypertension, and coronary artery disease [4]. Diagnosis and evaluation of patients are based on the patient's history, physical examination, imaging (CT, US), and cystoscopy findings.

4.1. Therapeutic Modalities

Transurethral resection of bladder tumors (TURBT) is both a diagnostic and therapeutic procedure done after finding a suspicious lesion during cystoscopy or positive cytology. A secondary resection is advised for patients presenting with pT1 tumor or in patients with high-grade tumor on initial resection [4]. Secondary resection has been shown to improve recurrence-free survival and progression-free survival of patients with NMIBC [8]. It had been shown that the optimal time for secondary resection performance is 2-6 weeks after the initial resection [9].

Application of immediate intravesical chemotherapy after TURBT is suggested. Intravesical chemotherapy helps in the destruction of remaining tumor cells that were overlooked and had shown to reduce recurrence rates [10]. Gudjónsson et al. had conducted a randomized controlled trial on 200 patients with NMIBC. The study

evaluated the effect of immediate intravesical chemotherapy after TURBT versus TURBT alone. The results showed that the recurrence rates after 4 years were lower (62%) in patients who received immediate intravesical chemotherapy compared to those who didn't receive the treatment (77%) [11]. When comparing the efficacy between different chemotherapeutic agents (e.g. mitomycin C, epirubicin, pirarubicin, and gemcitabine) it has been shown that most drugs have comparable results [12].

In 1976 Alvaro Morales a Canadian urologist tested topical BCG in the bladder. It was the first use of intravesical BCG against NMIBC [13]. In 1990 the FDA approved BCG as a local therapy for high-grade NMIBC [14]. The BCG is still considered the most effective immunotherapeutic agent against bladder cancer. The exact mechanism of BCG remains unclear, although it is known to have both a direct antitumoral effect and an immune-mediated antitumoral effect [15]. BCG is usually installed 2-4 weeks after TURBT.

4.2. Immune Checkpoint Inhibitors

In the last decade, immune checkpoint inhibitors have become standard therapy for a variety of malignancies. Before their introduction as an adjuvant treatment there hasn't been much progress in life-prolonging therapy for urothelial cancers in the past 30 years. The first-line treatment for locally progressed or metastatic UC is cisplatin-based chemotherapy [4]. Tumor cells of UC often overexpress PD-L1, which binds to PD-1 receptors on activated effector T cells, leading to suppression of T-cell action [16]. Nivolumab and pembrolizumab are PD-1 receptor inhibitors, whereas atezolizumab, avelumab, and durvalumab act by inhibiting PD-L1 on cancer cells. The above-mentioned drugs are approved for second-line therapy of patients who are ineligible or have failed to respond to platinum-based chemotherapy [17].

Atezolizumab and pembrolizumab have been approved as first-line therapy of PD-L1 positive patients who cannot receive platinum-based chemotherapy. The IMvigor211 study compared the safety profile and effectiveness of atezolizumab to chemotherapy in patients with locally progressive or metastatic UC whose condition continued to worsen after platinum-based chemotherapy. The patients received 1200 mg of atezolizumab or chemotherapy every 3 weeks. The median OS didn't change significantly between those who received atezolizumab (11.1 months) to those who

received chemotherapy (10.6 months). In addition, the ORR was similar as well (23% in the atezolizumab group vs 22% in the chemotherapy group). However, patients who received atezolizumab had fewer Grade ≥3 adverse events compared to those who received chemotherapy (20% vs 43%). As a result, it was concluded that while atezolizumab did not significantly increase OS when compared to chemotherapy, its safety profile was superior [18]. The KEYNOTE-361 trial evaluated pembrolizumab alone or together with chemotherapy to solely chemotherapy as first-line treatment for patients with progressive UC. According to the data, the combination treatment of pembrolizumab with chemotherapy did not substantially enhance PFS or OS when compared to chemotherapy alone (8.3 months vs 7.1 months and 15.6 vs 14.3 months respectively) [19].

The FDA recently approved avelumab as a maintenance medication for progressive UC that hasn't advanced after receiving first-line platinum-based chemotherapy. Immunotherapy is usually well-tolerated compared to chemotherapy and has lower side effects with improvement in quality of life. Typically patients with autoimmune disorders are excluded from immunotherapeutic trials due to potential worsening of their condition. Immunotherapy might be considered only in patients with advanced UC that failed to respond to other treatment modalities. Patients with autoimmune disorders who are receiving immunotherapy should be monitored regularly and should consult an immunologist. SAUL was an international safety study of atezolizumab treatment for locally progressive or metastatic UC that included patients who were ineligible for the IMvigor211 phase 3 trial, such as those with autoimmune conditions. 45% of the patients had Grade ≥3 adverse events, 8% discontinued the treatment due to toxicity. The ORR was thirteen percent and the median OS and PFS were 8.7 and 2.2 months respectively [20]. The study's findings backed up the use of atezolizumab in patients with progressive UC who were not eligible for clinical trials and had few therapy choices.

There hasn't been a study comparing the safety profile and effectiveness of the authorized ICIs that inhibit the PD-1 pathway. The choice of which agent to use largely depends on the patient and physician inclinations, type of insurance policy, and administration schedule [4].

4.3. Adverse Effects Of Immunotherapy

Adverse effects (AEs) of immunotherapy usually affect the gastrointestinal and respiratory tracts, however rarer toxicities such as cardiac and neurologic toxicities can also occur and may be fatal without proper monitoring and immediate recognition [21]. AEs are most common in the first six months of treatment, but they can present along the entire treatment course, and certain toxicities have been documented months after treatment has ended. [22]. Corticosteroids (1-2mg/kg of daily prednisone for 2 toxicities) are the mainstay of management of AEs and should be continued until improvement of symptoms, and then tapered over 4-6 weeks. Immediate discontinuation and administration of high-dose corticosteroids are indicated for life-threatening toxicities (grade ≥ 3). Administration of infliximab (5mg/kg) might be helpful in the management of toxicities that are resistant to corticosteroid treatment [4].

Fatigue is the most frequently reported side effect of ICIs treatment. However, the fatigue is usually mild and does not require discontinuation of treatment [23]. Dermatologic toxicities are also very common, affecting more than 30% of patients. Typically patients present with pruritus and maculopapular erythematous rash over the trunk and extremities. Severe dermatological toxicities such as *Stevens-Johnson Syndrome* or *Toxic Epidermal Necrolysis* have been reported but rarely occur [24]. Other AEs of ICIs include diarrhea, hepatotoxicity (elevated liver enzymes and bilirubin), pneumonitis, hypothyroidism, and less commonly adrenal insufficiency, type 1 diabetes mellitus, kidney damage, myocarditis, and neuropathies [25,26].

5. Renal Cell Carcinoma

Renal cell carcinoma (RCC) is responsible for 2% of all cancer diagnosis and deaths worldwide. In the industrialized world it is more prevalent, and in the United States it is the ninth most prevalent cancer [27,28]. Most cases are detected incidentally on imaging because symptoms typically present at an advanced stage of the disease which results in a poor prognosis. 30% of patients present with metastasis at diagnosis with a 5-year survival rate of only 12% [29]. Men are more likely to develop RCC (2/3 of cases), and the median age of diagnosis in the United States is 64. The most

frequent histological type of renal cell carcinoma is clear cell renal cell carcinoma (ccRCC), which accounts for around 75% of all cases. Other histological types include papillary RCC (20%), chromophobe RCC (5%), and other rarer types such as medullar RCC, translocation associated RCC, and collecting duct RCC [30].

Immunotherapy with cytokines such as interleukins and interferons were previously used as the standard treatment of metastatic RCC, however, due to poor results, their use has diminished [31]. There has been a significant improvement in PFS and OS through the use of tyrosine kinase inhibitors (TKI) [32]. According to the Checkmate 214 trial, the combination treatment of nivolumab plus ipilimumab had a significantly higher OS and ORR compared to nivolumab plus sunitinib, for the treatment of advanced ccRCC (75% vs 60% and 42% vs 27% respectively) [33]. Resistance to ICIs is a big obstacle, it can be primary (innate) or secondary (acquired). Multiple pathways, such as neo-antigen loss, antigen presentation failure, faulty interferon signaling, might lead to the development of resistance. Identification of biomarkers in a subpopulation of patients is crucial for the selection of ideal treatment and improvement of OS. In patients with metastatic ccRCC, ICIs in conjunction with TKIs are now used as a therapeutic approach. The FDA has approved pembrolizumab (anti-PD-1) plus axitinib as first-line treatment, after the Keynote 426 trial showed an encouraging result of OS at 12 months follow up (90% vs. 78%; HR: 0.53; CI: 0.38–0.74; $p < 0.0001$) [34]. The IMDC risk model guides physicians in the determination of treatment strategy. It is important to take into consideration the patient's comorbidities and age as it might affect their prognosis and treatment plan, it's critical to verify the safety profile of ICIs before starting treatment.

5.1. Drugs in Ongoing Trials

Lymphocyte-associated gene 3 (LAG3) is expressed on activated T cells and natural killer cells. The number of interferon-gamma, tumour necrosis factor-alpha, and other pro-inflammatory interleukins are all enhanced when LAG3 is inhibited [35]. T cell immunoglobulin and mucin domain3 (TIM3) is a set of molecules found on several immune cells that function as a negative regulators of immunological checkpoint by upregulating apoptosis [36]. Blocking the TIM-3 pathway enhances cancer immunity and increases the production of interferon-gamma (IFN-γ) in T cells and NK cells

[37]. Several preclinical trials investigating the TIM-3 pathway blockade have reported promising improvements in the outcome of cancer patients.

The v-domain immunoglobulin suppressor of T cell activation (VISTA) is a new negative checkpoint ligand that suppresses T-cell activation in the same way that PD-L1 does. Antigen-presenting cells (APC) and myeloid-derived suppressive cells are the most common sites where VISTA is found. VISTA blockade by monoclonal antibody treatment had increased anti-tumor immunity in transplantable tumor models. It was found to enhance the number of T cells and dendritic cells infiltrating the TME while decreasing the amount of regulatory T cells and myeloid-derived suppressor cells. The study data concluded that VISTA could present within the TME of multiple solid tumors that are infiltrated with myeloid cells and T cells, indicating that VISTA-blockade therapy might be applicable in multiple types of tumors [38].

T cell activation in the TME is also mediated by co-stimulatory signals. The effects of several co-activating immunological checkpoints are being studied in a number of active clinical trials. CD28 is found-on T cells, and when binding CD80/86 on APCs it initiates a co-stimulatory effect required for T cell activation and survival. Another example is the Inducible co-stimulator (ICOS), which is predominantly found on CD4 T cells and like CD28, it has a co-stimulatory effect. ICOS induces lymphocyte proliferation and the production of proinflammatory cytokines [39]. Another potential receptor is the OX40, also known as CD134, which stimulates T cell generation and continuity by enhancing the production of proinflammatory cytokines and molecules that prevents apoptosis [40].

5.2. Predictive Biomarkers

Carbonic anhydrase IX and vascular endothelial-derived growth factor are the most prominent biomarkers in RCC, and they are used as excellent predictors of treatment response. Other biomarkers such as CXCL16, ADAM10, and P53 are used in integrated staging systems [41].

PD-L1 is the most widely known immunohistochemical biomarker, however, it is not a highly reliable predictor for metastatic RCC. Given the heterogeneity of RCC (in the primary tumor, as well as between the primary site and metastatic sites) it is

extremely difficult to find a reliable means of determining prognosis and optimal therapy [42].

In patients with advanced RCC, Tumour Mutational Burden (TMB) is a possible predictive biomarker for immunotherapy response. TMB is based on the overall number of mutations in a tumor genome's coding region. When the TMB is high there is increased formation of neo-antigens which induces an immune response. A high mutational load was associated with an improved response in patients treated with ICIs in other types of cancers (metastatic melanoma and non–small cell lung cancer) [42].

Loss of Mismatch Repair (MMR) is commonly observed in RCC. These tumors tend to have a higher mutation burden on specific genes, however, MMR status as an indicator for immunotherapeutic response in RCC is still being researched [43].

Interestingly the gut microbiome seems to affect the response to ICIs. The gut microbiome is composed of bacteria and archaea, and its composition depends on genetic and environmental factors. Derosa et al. discovered that patients with metastatic RCC who were given antibiotics within a month of starting treatment had a worse survival rate than those who were not given antibiotics. While other bacteria, like B. salyersiae and A. muciniphila had been shown to restore the function of ICIs [44].

5.3. Prospective Modalities and Technologies

Multiple research on immunological populations has discovered a link between the number and kind of invading immune cells and cancer patient prognosis. By using transcriptomic markers, the microenvironment cell population counter (MCP-counter) technique estimates the abundance of tissue-infiltrating immune and stromal cell populations in the tumor microenvironment. MCP-counter has the potential to be employed in clinical practice to quantify immune cell infiltration in tumor tissues where immunohistochemical techniques, such as fine-needle aspiration, are not possible. The MCP-counter method could aid clinicians in predicting a patient's prognosis or reaction to treatments, as well as personalizing treatment regimens [45].

Single-cell RNA sequencing is a relatively new technology used to analyze intra-tumor heterogeneity by characterizing individual cells within the tumour and

metastatic sites. RCC is known to have considerable variability in tumour composition, and this technology can help better characterize cell populations and discover new biomarkers [46].

A functional ex vivo tumor culture derived from tumor samples, which closely resemble in vivo TME, is investigated for potential use in drug testing and response prediction. These 3D model systems are based on tissue samples with preserved components of TME, and could potentially help monitor immunotherapeutic response and establish personalized therapy. This method is already used in TKI targeted therapies, and it allows researchers to better understand immune escape mechanisms and find new predictive biomarkers [47,48].

Circulating tumour cells (CTC) is an important tool for the early detection of cancer. The standard way of detecting CTCs is by the use of an EpCAM (epithelial cell adhesion molecule) based enrichment strategy; however, this method does not perform well for tumors with minimal EpCAM expression, such as RCC. A new set of cell surface markers, such as Carbonic anhydrase 9 (CA9) and CD147 were developed to improve the detection of CTCs in patients with RCC and had shown to have significant results [49]. CTCs analyses could be used in the diagnosis and prognosis of RCC, and aid in the development of personalized therapeutic strategies for selected patients.

Targeted immunotherapy for metastatic RCC is rapidly evolving and it provides an increasing number of therapeutic options. Single-cell RNA sequencing and circulating tumour cells (CTC) detection are an example of two new technologies that are assisting physicians in unraveling intratumoral heterogeneity, discover predictive biomarkers, and identify new therapeutic methods.

6. Prostate Cancer

In the developed world, prostate cancer is the most prevalent non-skin cancer diagnosed in men. The majority of cases present as localized lesions; nevertheless, recurrences typically occur in about thirty-five percent of cases. Clinically the lesions can range from insignificant histologic cancers to aggressive lethal tumors with rapid progression. The most significant risk factor is age, with 66 being the average age of

diagnosis. The incidence of prostate cancer increases from 20% in men in their 50s to approximately 70% in men between the ages of 70 and 80 years. Exposure to carcinogens, estrogens, consumption of red meats, being overweight, a history of cancer in one or more family members, and race are all risk factors for prostate cancer. Genetic mutations such as MYC and HOXB13 germline mutations, mutations in BRCA2, and Lynch syndrome have been proven to enhance the chance of acquiring prostatic cancer [50].

Prostate tumors tend to show substantial histomorphological and molecular diversity between different patients and within a given tumour [51]. More than 80% of primary prostate cancers present with multiple topographically and histomorphological distinct tumour foci [52], which increase the complexity of the disease. Genomic sequencing demonstrates high levels of genomic diversity between patients, within a given primary tumour, and even within different metastatic sites [53].

Castration or treatment with antiandrogens are used to induce disease regression, however, most tumors eventually develop resistance to this method of treatment through various mechanisms. One of which is the development of hypersensitivity to low levels of androgens through AR gene amplification. In 70% of cases, prostate cancer develops in the peripheral zone of the gland, usually posteriorly, where it may be detected by rectal examination [54].

The most fatal kind of prostate cancer is metastatic castrate resistant prostate cancer. Combination immunomodulatory techniques including vaccine-based treatments, chimeric antigen receptor (CAR) T cells and checkpoint inhibitors are now being evaluated in a number of clinical trials. In addition, a number of studies are examining the efficacy and safety of combining immunotherapy with traditional treatments such as androgen deprivation therapy, taxane chemotherapy, radiation, targeted TKIs, and PARP inhibitors. [55].

In individuals with metastatic disease, androgen deprivation therapy (ADT) enhances overall survival by about two and a half years [56]. Orchiectomy and GnRH receptor agonists/antagonists can be used as ADT techniques. For the treatment of metastatic hormone sensitive prostate cancer (mHSPC), first-line medicines such as abiraterone acetate, apalutamide, and enzalutamide, as well as docetaxel chemotherapy, are commonly used in conjunction with ADT [57]. Sipuleucel-T is cell-based cancer

immunotherapy designed to invoke a T cell response to prostatic acid phosphatase (PAP), and is used to treat mCRPC based on the pivotal phase III IMPACT trial [58].

In comparison to other diseases such as melanoma or non-small cell lung cancer, ICIs had shown to have a limited efficacy in the treatment of prostate cancer [59]. This might be due to the low tumor mutation burden (TMB) seen in CRPC, which results in low immunogenicity due to a smaller pool of neoantigens [60,61]. Another potential reason for the poor response to ICIs might be the chronic inflammatory state which results in immunosuppressive TME [62,63]. There is a subset of patients who present with a sustained response to ICIs, these patients typically have a high intratumoral cluster of differentiated CD8 T cell density, high IFNγ response, and antigen-specific T cell response [64].

Biomarkers are a useful clinical indicators and can help guide treatment strategies in patients with prostate cancer. For instance, patients with persistent neutrophil to lymphocyte ratio greater than 3 under enzalutamide therapy had shown to have a favorable clinical outcome, while androgen receptor splice variant-7 (AR-V7) gene expression was associated with enzalutamide and abiraterone resistance [65]. Based on these results clinicians could potentially tailor a specific treatment regimen for the patient.

6.1. Vaccine-Based Therapies

Vaccine-based therapies are used to treat existing cancers by stimulating the immune system. They are broadly divided into four major categories: DNA-based vaccines, peptide-based vaccines, viral vector-based vaccines, and cell-based vaccines.

DNA-based vaccines expose the immune system to epitopes from the target pathogen, which allows the immune system to develop antibodies. Plasmids are taken up by the host cell, which then synthesizes tumor-associated antigens (TAAs). These TAAs lead to an immune response against the tumor. The pTVG-HP and pTVG-AR vaccines, which promote the synthesis of human PAP and AR antigens, are two examples of DNA-based immunizations [66].

Peptide-based vaccinations are composed of antigen epitopes that are delivered to the host's APCs. The UV1, for example, comprises the human telomerase reverse transcriptase (hTERT) and granulocyte-macrophage colony stimulating factor (GM-

CSF). UV1 is currently being tested in a phase II clinical trial for mHSPC patients. [67].

Viral vector-based vaccines use a viral vector to transfer a TAA into the patient and thus induce an immune response. An example includes PROSTVAC, which encodes PSA and generates a T-cell response, it includes two live poxviral-based vectors: PROSTVAC-V and PROSTVAC-F. In addition to the PSA, TRICOM is a fowlpox virus vector that encodes ICAM-1, B7-1 and LFA-3 which are costimulatory molecules that may improve antigen presentation and activate cytotoxic T-cells [68].

Cell-based vaccines use whole tumor cells as an antigen source. In order to trigger the development and differentiation of dendritic cells, a polyvalent supply of antigens is frequently coupled with GM-CSF [69]. The GVAX-PCa vaccine is a prime example, it is made up of two allogeneic prostate cancer cell lines, however VITAL-1 and VITAL-2 phase III trials didn't show a clinical benefit to this vaccine. Sipuleucel-T is an autologous cell-based vaccination generated of peripheral blood mononuclear cells (PBMCs) that has been approved to treat mCRPC. Sipuleucel-T increased the OS in individuals with mCRPC by 4.1 months in the phase III IMPACT study when compared to placebo [70].

6.2. Immune Checkpoint Inhibitors

A group of patients with mCRPC who had a high PD-1/PD-L1 expression level benefited from ICIs therapy in the CheckMate 650 clinical trial [71]. PD-L1 expression has shown to be upregulated in higher-stage tumors with lymph node involvement. In addition, adjuvant treatment with enzalutamide has also been shown to upregulate PD-L1 expression in preclinical models [72]. Ipilimumab is an anti-CTLA-4 monoclonal antibody, which binds and inhibits the CTLA-4 receptor on T lymphocytes. The inhibition of the CTLA-4 receptor thus allows T cell stimulation and results in increased anti-tumor immune response [73]. However, phase II clinical trials (NCT00861614, NCT01057810) showed that patients with mCRPC didn't have a significant increase in OS when treated with ipilimumab [74]. Interestingly, the phase III trial CA184-043, which evaluated the response to radiotherapy followed by ipilimumab compared to placebo in patients with mCRPC, revealed that the OS

increased two times in patients who were given ipilimumab for 3 years or more, which indicates a long-term immune benefit [75].

According to phase Ib KEYNOTE-028 and phase II KEYNOTE-199 clinical trials, pembrolizumab did not have a significant response in patients with mCRPC. The objective response rate (ORR) in PD-L1 positive patients was 5%, compared to 3% in PD-L1 negative patients [76]. Pembrolizumab was approved in the treatment of individuals who do not have other treatment choices and have a defective mismatch repair (dMMR) mechanism. When ICIs are used in patients with dMMR, a stronger immune response typically occurs due to the larger number of neo-antigens that present in these patients [77]. Ipilimumab and nivolumab combination therapy had shown efficacy in phase II trial, with 25% ORR in patients with AR-V7 positive metastatic prostate cancer [78]. Another PD-1 inhibitor, cemiplimab, is used to treat individuals with malignant squamous cell carcinoma. Cemiplimab in combination with new drugs like the mRNA vaccine W pro1 (mRNA vaccine) is currently being tested in clinical trials for the treatment of prostate cancer patients. TME research revealed that a TME that expresses a high number of immune-suppressive factors such as TGF, Tregs, HIF-1, PD-L1, and IL-10, was linked to a poor prognosis and increased resistance to ICI therapy [79]. Furthermore, low immuno-stimulatory factors, such as reduced levels of T-cell receptor zeta (TCR ζ) on peripheral lymphocytes [80], reduced number of circulating NK cells, and mutated HLA expression, have been shown to increase tumor-immune evasion [81,82].

6.3. Ongoing Clinical Trials

There are currently ongoing clinical trials that evaluate the combination therapy of certain vaccines with ICIs for patients with mCRPC [83]. The ChAdOx1-MVA 5T4 vaccine is made up of two replication-deficient viruses that attack the "oncofetal self-antigen 5T4". This antigen is expressed on many different tumor cells and was found to induce 5T4-specific T cell responses in phase I clinical trial [84]. In a phase II clinical trial, the combination of the pTVG-HP and pTVG-AR vaccines with pembrolizumab is being investigated [85]. Another vaccine that is in an ongoing clinical trial is the Wpro1. Wpro1 is an mRNA vaccine combined with liposomes, and it encodes five antigens that are found in prostate cancer, which stimulates an antigen-specific T cell response. These mRNA-based vaccines could potentially replace the

conventional vaccine therapies due to their capacity for rapid development, relative low-cost, and safe administration [86].

The combination therapy of ICIs with tyrosine kinase inhibitors (TKIs), such as sunitinib, cabozantinib, and axitinib, had displayed a synergistic effect in the treatment of some malignancies, such as renal cell carcinoma [87]. TKIs play a role in the inhibition of VEGF, which prevents tumor angiogenesis. Furthermore, TKIs also reduce the immune inhibitory effects of Tregs and MDSCs [88]. The combination of cabozantinib and atezolizumab was tested in the COSMIC-021 phase 1b clinical study in patients with mCRPC. The results showed a 32% ORR and an 80% illness control rate [89].

The KEYNOTE-921 phase III clinical trial is currently evaluating the role of combination therapy with pembrolizumab and docetaxel in patients with mCRPC. Similarly, the CheckMate 9KD clinical trial has recruited patients with mCRPC to evaluate the combination therapy with nivolumab and docetaxel. Despite the fact that chemotherapy normally suppresses the immune system, there is evidence that it can stimulate anti-tumor immunity via boosting antigen presentation and costimulatory molecules [90].

Evidence suggests that a combination of targeted radionuclide therapy (TRT) with ICIs may increase T cell infiltration in tumors. A phase II trial is assessing the efficacy of combining “Lutetium-177 Prostate-specific membrane antigen-617” and pembrolizumab therapy in individuals with mCRPC. The use of ICIs in combination with PARP inhibitors has been demonstrated to have a synergistic effect in the treatment of cancers, particularly those with a homologous recombination defect (HRD). This combination therapy induced an increase in intratumoral CD8 T cell infiltration, local IFN production, and upregulation of PD-L1 expression [91]. PARPs are enzymes that catalyze the addition of poly ADP-ribose and are involved in cell signaling and DNA repair. The FDA has approved PARP inhibitors for the treatment of breast and ovarian malignancies [92,93,94]. Based on the phase II TRITON2 and phase III PROFOUND clinical studies, Rucaparib and Olaparib were approved for the treatment of homologous recombination castrate resistant prostate cancer [95,96].

7. Testicular Germ Cell Tumors

Testicular cancer is a relatively uncommon cancer, accounting for less than 2% of cancers in men. Most commonly diagnosed in young men between ages 15 and 35. About 95% of all testicular cancers arise from germ cells. Testicular germ cell tumors (TGCTs) can be classified into seminomas or non-seminomas, based on histological examination. Some of the major risk factors include Caucasian ethnicity, undescended testicle, family history of testicular cancer, HIV infection, and abnormally developed testicles [97].

TGCTs are usually highly treatable, especially due to their sensitivity to cisplatin-base chemotherapy. Treatment is determined by the histological subtype and stage of the disease, with orchiectomy and surveillance being the primary means of treatment in most patients. In cases of metastatic disease chemotherapy alone or combination with surgery and radiotherapy can be used [98,99]. Around 20% of individuals with metastatic illness will relapse after first treatment, although salvage high dose chemotherapy can put half of these patients into remission [100]. Patients with cisplatin-refractory disease or patients who have relapsed after second-line chemotherapy can be treated with biological therapies, such as sorafenib, pazopanib, everolimus, sirolimus, and brentuximab [101].

7.1. Basis for Immunotherapy in TGCTs

Spontaneous regression of primary TGCT, also known as “Burned out”, is an uncommon phenomenon in which there is complete or partial regression of TGCT without any intervention, leaving a scar in the parenchyma [102]. It's assumed to be caused by the host's immune response to cancer/testis antigens (CTAg), which is mediated mostly by CD8+ and CD4+ CTAg-specific T-cells. When compared to normal testis or inflammatory lesions, the TME of TGCTs has been demonstrated to have a different immune cell makeup [103]. Fankhauser et al. looked at the degree of PD-L1 expression in TGCTs to see if they could be targeted by immunotherapeutic drugs. According to his findings PD-L1 expression was shown to be elevated in 73% of all investigated seminomas and 64% of all non-seminomas, but not in normal testicular tissue. These elevated levels of PD-L1 expression in TGCTs could indicate that PD-L1 inhibitor treatment might be beneficial in the management of TGCT

patients [104]. Patients with higher PD-L1 expression in the primary tumor had poorer PFS and OS, whereas individuals with lower PD-L1 expression had better PFS and OS [105].

A retrospective cohort study on 164 patients with TGCT evaluated the prognostic value of several hematological markers. The findings showed that a high neutrophil-to-lymphocyte ratio (NLR>4) and high absolute neutrophil counts (>8,000/L) were linked to progressive illness and mortality [106]. In patients with TGCT, researchers looked at how much PD-L1/CTLA-4 and mismatch repair (MMR) proteins were expressed in invading immune cells (ICs). PD-L1/CTLA-4 positivity was seen in the majority of patients, regardless of the histological subtype, however, CTLA-4 expression was shown to be significantly greater in yolk sac tumors, teratomas, and choriocarcinomas. Patients who exhibited negative or low PD-L1/CTLA-4 expression in ICs correlated with worse relapse-free survival (RFS) and had worse prognostic features [107].

Siska et al. had conducted a study with the goal to find new prognostic indicators for TGCTs through immune profiling using multiplexed fluorescence immunohistochemistry (FIHC) for T-cells and immunological checkpoints. Patients with higher levels of infiltrating CD3+ T-cells, high levels of PD-L1 expression, and increased PD-1/PD-L1 spatial interaction had a better prognosis, whereas advanced disease stage was linked to lower T-cell and NK-cell expression, as well as elevated Treg, neutrophil, mast cell, and macrophage genes. These results suggest that immune profiling for prognostic markers, and the incorporation of anti-PD-1/PD-L1 drugs, could potentially be beneficial for patients with TGCTs [108].

7.2. Immune Checkpoint Inhibitors In The Treatment Of TGCTs

A single-arm phase II trial evaluated pembrolizumab in 12 patients with platinum-refractory TGCTs. Eligible patients (age ≥18) had TGCTs that has progressed after first-line cisplatin-based chemotherapy or after at least one salvage regimen of high-dose chemotherapy. Six patients had a late relapse (>2 years), and six grade 3 adverse events were reported. Only two patients attained radiographic stability for a few weeks, but none of them showed signs of partial or complete remission. These results

indicate that pembrolizumab does not have a meaningful effect on patients with platinum-refractory TGCTs [109].

In a case report, pembrolizumab was used in a 27-year-old male patient with metastatic choriocarcinoma. The patient presented with a large left pelvic mass, 2 hemorrhagic brain lesions and metastasis in the mediastinum and lungs. A left radical orchiectomy and retroperitoneal lymph node dissection were performed. The patients had relapsed after 3 cycles of high-dose chemotherapy and an autologous peripheral-blood hematopoietic stem cell transplant (PBSCT). The patient was enrolled in a phase II clinical research that evaluated how well pembrolizumab worked in individuals with platinum-resistant TGCTs. However, his treatment was terminated after one cycle of pembrolizumab (200 mg IV) due to rapid disease progression and he passed away a month later [110].

The combination treatment of durvalumab (PD-L1 inhibitor) with tremelimumab (CTLA-4 inhibitor) was evaluated in another phase II clinical trial. The research examined 22 people who had advanced germ cell cancers. Out of the 22 patients recruited only two patients achieved partial response, with reduction of serum tumor marker and stabilization of the disease, while the rest exhibited disease progression [111].

In a phase II multicenter trial, Avelumab was investigated in 15 patients with single-agent chemotherapy refractory gestational trophoblastic tumors (GTT). The patients received avelumab 10 mg/kg IV every 2 weeks until hCG levels normalized. Avelumab had alleviated chemoresistance in half of the patients and had a good safety profile [112].

Nivolumab is another PD-L1 inhibitor that has been authorized for the treatment of patients with metastatic melanoma, lung carcinoma, RCC, Hodgkin lymphoma, urothelial carcinoma, gastric carcinoma, and hepatocellular carcinoma, among other cancers. Chi et al. evaluated a patient with metastatic choriocarcinoma who was treated with nivolumab after all other treatment options, such as several lines of chemotherapy, stem cell transplant and radiotherapy, were exhausted. The patient achieved partial radiographic control after fourteen months of therapy [113].

Brentuximab-vedotin (BV) is an antineoplastic chemotherapeutic drug, that is made of a chimeric monoclonal antibody (cAC10) which is linked to monomethyl auristatin

E (MMAE). The cAC10 antibody binds the CD30 receptor on tumor cells and delivers the MMAE, which is responsible for the anti-tumour activity.

Albany et al. published a case series about 7 patients with refractory CD30 expressing TGCTs who were treated with Brentuximab Vedotin (BV). The patients received BV with an initial dose of 1.8-2.4 mg/kg every three weeks. After four cycles of treatment, one patient had a complete response, while the other had a partial response after two cycles of treatment. BV therapy was well tolerated and had durable responses, thus it may be potentially used to treat patients with refractory testicular cancers [114].

Different ICI drugs, such as T-cell immunoglobulin and mucin domain-3 (TIM-3) inhibitors or immunological checkpoint lymphocyte activation gene-3 (LAG-3) inhibitors, have been demonstrated to have synergistic action in the treatment of various cancers when used with anti-PD-1 drugs. In addition, the combination of TIM-3 inhibitors or LAG-3 inhibitors with anti-PD-1 agents has been shown to help overcome resistance to anti-PD-1 therapy [115, 116].

Overall according to the above-mentioned data it was conclude that ICIs play an insufficient role in combating TGCTs. This might be due to the physiologically suppressed immune TME that is characteristic in testicular tumors. Another potential reason might be the low tumor mutation burden typically seen in TGCTs [117].

8. Upper Tract Urothelial Carcinoma (UTUC)

Upper tract urothelial carcinomas (UTUCs) are carcinomas that arise from the inner lining of the renal pelvis, calyces, and ureters. UTUC is a rare disease, accounting for less than 10% of all urothelial carcinomas [118]. At the time of diagnosis, approximately 60% of patients display advanced muscle-invasive illness, with a five-year survival rate of 75% [119]. Men are 3 times more likely than women to have UTUC, and it is much more common in the elderly (above 70 years of age). The major risk factors are smoking tobacco products, exposure to aromatic amines, ingestion of arsenic, and chronic inflammation due to recurrent UTIs [120]. Several genetic diseases, such as Lynch syndrome (hereditary nonpolyposis colorectal cancer), are linked to an increased risk of UTUC [121].

8.1. Diagnosis Of UTUC

In individuals with UTUC, haematuria is the most prevalent symptom, occurring in 80% of cases. Patients with visible haematuria are more likely to be diagnosed with UTUC than those with nonvisible haematuria [122]. Other symptoms include anorexia, weight loss, fatigue, urinary frequency or urgency, dysuria, flank pain, lumbar mass, and night sweats [123].

The most accurate imaging technique for diagnosing UTUC is CT urography, which provides high-resolution images, remarkable levels of specificity (93%-99%), and high levels of sensitivity (67%-100%) [124]. MRI is less favorable in comparison to CT due to its lower spatial resolution, reduced ability to identify small non-obstructing urinary calculi, motion artifacts, higher cost, and longer time to acquire results. MRI is mostly reserved for patients with contraindications for ionizing radiation or IV contrast.

Messer et al. evaluated the diagnostic accuracy of urine cytology for detecting advanced UTUC and found that urine cytology has poor sensitivity and positive predictive value for detecting UTUC compared to bladder carcinoma [125]. Urine cytology has lower sensitivity for detecting low-grade UTUC as compared to high-grade UTUC, mainly due to the overlapping morphological characteristics of low-grade UTUC and reactive urothelial cells [126]. Site-directed collection performed endoscopically from the renal pelvis or ureteral lumen had shown to increase sensitivity for detecting both high-grade (69% sensitivity, 85% PPV) and muscle-invasive UTUC (76% sensitivity, 89% PPV) [127].

Ureteroscopy can be used to visualize the entire upper urinary tract in order to detect and acquire a biopsy from cancerous lesions. However the downside for this diagnostic approach is the risk of intraluminal tumor seeding and intravesical recurrence (IVR), therefore the European Urology Association (EAU) recommends ureteroscopy only if imaging and cytology are not sufficient for establishing a diagnosis.

UTUC may appear differently on imaging, depending on its stage, location, and imaging modality used. Large papillary lesions or wall thickening are typically more visible on the excretory phase, while focal enhancement or infiltrative lesions are

more accurately identified on the parenchymal phase. Dilated calyces, hydronephrosis, cystic masses, and lymphovascular invasion are associated with more advanced disease. If the disease is located within the ureters, it may present as abnormal thickening, strictures, or as focal masses [128].

8.2. Treatment Modalities Of UTUC

Flexible Ureteroscopic ablation is considered a safe kidney-sparing treatment modality in patients with low-risk disease (unifocal, <2 cm in size, low-grade cytology, and biopsy, non-invasive), especially in pelvicalyceal tumours, or when patients have imperative indications (solitary kidney, severe renal insufficiency, bilateral disease, Lynch syndrome) [129].

Ureteroscopic laser ablation uses infrared lasers (e.g. Holmium: YAG, Thulium: YAG) which have low tissue penetration, and thus help reduce the risk of bleeding from papillary tumor vessels [130].

The gold standard for UTUC therapy is radical nephroureterectomy (RNU). Laparoscopic RNU is a minimally invasive surgical procedure in which the renal pelvis, kidney, ureter, and the bladder cuff are removed. Presurgical chemotherapy is given to selected patients, pending the result of their tumor biopsies, which provide important information on the tumors size, grade, and location.

Cisplatin-based neoadjuvant chemotherapy (NAC) might be administered before RNU in patients with adequate renal function and with high-grade tumors on biopsy. While performing RNU it is important not to enter the urinary tract in order to avoid tumor seeding into the bladder. Intravesical mitomycin C (MMC) instillation for 1 hour during surgery has been found to minimize the incidence of intravesical recurrence during the first year following surgery [131]. Minimally invasive (MIS) approaches, such as laparoscopy, are preferable compared to open surgery, and have shown to have fewer morbidities and similar oncological outcomes.

Kidney-sparing surgery (KSS) is used in patients with poor renal function, comorbidities, those with a high risk of bilateral disease, or in selected patients that present with low-risk disease. The big downside of KSS is the high risk of cancer recurrence. Intracavitary instillations of BCG are the most common topical agent used

after KSS. Other important topical agents include Mitomycin C, Thiotepa, and Epirubicin [132].

Kojima et al. evaluated the effectiveness of nephroureterectomy versus BCG in patients with UTUC. A retrospective analysis of the post-treatment period of 17 patients with CIS of the upper urinary tract who received either nephroureterectomy or BCG treatment found that both groups had similar 5-year RFS, implying that BCG therapy is as effective as nephroureterectomy for CIS of the upper urinary tract [133].

The most common method for intracavitary instillation of topical agents in the upper urinary tract is by a large nephrostomy tube. This anterograde approach allows an optimal contact duration between the topical agents and the upper urothelium. The downside of this approach is the risk of recurrence as a result of tumour cell seeding. Retrograde approaches for delivering these topical agents are performed either by "transvesical ureteric catheterization" or by "vesico-renal reflux approach", which uses an indwelling double-J stent to create a passive retrograde reflux from the bladder [134].

8.3. Adjuvant Chemotherapy Vs Surveillance

The POUT phase III control study compared the use of adjuvant chemotherapy to surveillance alone in UTUC patients. Patients with resected non-metastatic UTUC were put on either four cycles of gemcitabine with platinum-based chemotherapy or put on surveillance. The results reported an improvement in disease free survival (DFS) in both chemotherapy regimens (70% in chemotherapy versus 51% in surveillance) and reported a significant increase in PFS in all patients who received adjuvant chemotherapy [135]. It is difficult to establish which patients would likely benefit from adjuvant chemotherapy because different subtypes of UTUCs have been shown to respond differently to chemotherapy. For instance, UTUC with variant histology other than pure UC has shown to be less responsive to chemotherapy, while hereditary forms of UTUC had shown to have a better outcome after adjuvant chemotherapy as compared to sporadic forms (48.2% versus 32%) [136]. The POUT trial results would likely affect the future guidelines in favor of adjuvant chemotherapy for patients with UTUC as a result of their efficacy.

8.4. Immune Checkpoint Inhibitors In UTUC

ICIs had recently gained popularity in the management of genitourinary carcinomas in patients who are cisplatin-ineligible or those with refractory disease after several chemotherapeutic rounds. Despite the fact that cisplatin-based combination chemotherapy is the initial treatment modality for urothelial carcinomas, a significant number of patients are unable to receive it due to comorbidities such renal failure, congestive heart disease, and hearing loss [137]. In addition, 21% of cisplatin-ineligible patients who are put on carboplatin-based regimens or carboplatin plus gemcitabine, discontinue the treatment due to adverse events.

Pembrolizumab has a low risk of side effects and is approved for the treatment of urothelial carcinoma patients who are unable to tolerate chemotherapy. In the KEYNOTE-045 phase III study, pembrolizumab was compared to chemotherapy as second line treatment in patients with progressive UC, and pembrolizumab was found to improve overall survival (10 months compared to 7 months), and had lower treatment-related adverse events [138].

Pembrolizumab as a first line treatment modality for patient with locally advanced or metastatic UC of the renal pelvis, ureter, bladder, or urethra was explored in the KEYNOTE-052 clinical trial. Patients were given 200 mg of pembrolizumab every 3 weeks for a total of 24 months, or until disease progression, pregnancy, or non-compliance forced them to stop the therapy. Out of 370 patients who received the treatment, 89 (24%) had an objective response, with 72 patients having a partial response, and 17 patients having a complete response. 233 (63%) patients had to discontinue the treatment with a median treatment time of 3 months. Disease control was observed in 173 patients (47%) and disease progression was noted in 248 patients, out of which 130 deaths were recorded, with a median PFS of 2 months (95% CI 2–3) [139].

Overall pembrolizumab had shown to have substantially better tolerability in comparison to chemotherapy (gemcitabine or methotrexate plus carboplatin) in cisplatin-ineligible patients, with only 5% of patients which had to discontinue the treatment due to adverse events. Pembrolizumab has the advantage of being able to be utilized in patients with impaired renal function.

This trial also evaluated the relationship between PD-L1 expression and response rates. Immunohistochemical assays were used to assess PD-L1 expression in cancer cells and inflammatory cells, and a combined positive score was obtained (CPS). Patients with a CPS of more than 10% had the highest response rates, whereas patients with low or no PD-L1 expression still responded but at a lower level. The results showed that first-line pembrolizumab provides an excellent clinical result and a longer OS in patients with progressive UC who are ineligible for cisplatin chemotherapy [139].

To date, advanced UTUC is considered a terminal disease with an estimated survival of only a few months. Immunotherapy for UTUC still lacks enough evidence and more trials need to be published in order to improve the level of care for these patients.

9. Conclusion

Multiple current clinical trials evaluating the safety and efficacy of ICIs in the treatment of various genitourinary cancers have yielded promising results. The management of bladder cancer in particular already incorporates ICIs in the new treatment paradigms. Patients with metastatic UC had shown to have good tolerance to ICIs as compared to chemotherapy, with lower side effects and improved quality of life.

It is hard to predict which patients would likely respond to ICI treatment. In some studies, the level of PD-L1 expression did not show a direct correlation to ICI treatment response. There is a need to better identify patients who would likely benefit from ICI therapy. Further investigation of predictive biomarkers could help stratify patients and help us develop personalized treatment plans.

Currently, no ICIs have been shown to increase OS in advanced prostate cancer, except pembrolizumab in patients with dMMR, and ipilimumab [76]. Novel combination of chemotherapeutic agents with ICIs may act synergistically and potentially transform “cold” unresponsive tumors to immunologically responsive “hot” tumors. Additional investigations are required in order to improve immunotherapy in prostate cancer.

ICIs were not able to enhance the outcome in patients with refractory TGCTs, according to published case reports and the results of phase II clinical studies. This might be due to the immune tolerance and the low mutation burden that are characteristic of germ cell tumors.

To date, there isn’t sufficient data on immunotherapy in UTUC due to the low incidence rates. Ongoing clinical trials and new technologies contribute to our understanding of tumor heterogeneity, identification of predictive biomarkers, and the discovery of new treatment options for patients with advanced genitourinary malignancies.

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