Efficacy and Safety of Novel Immunotherapy Agents in High-grade Urothelial Carcinoma

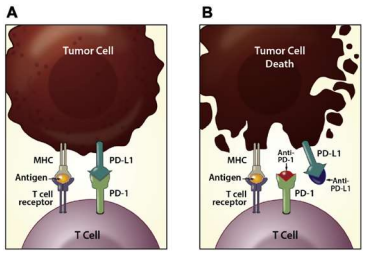
Rachel Smith, MMS, PA-S
Amanda Seymour, PA-C
Department of Medical Science

Abstract

Urothelial carcinoma (UC) treatment largely relies on surgery and platinum chemotherapies. Unfortunately, platinum chemotherapies have adverse effects (AE) that result in discontinuation and ineligibility of therapy. Novel immunotherapies have been found to have not only a safer treatment profile versus platinum chemotherapy, but are also efficacious in the treatment of in high-grade UC.

Introduction

UC is largely found in the transitional cells of the bladder, ureters, urethra, and renal pelvis. UC is the 9th most common cancer globally with high mortality and a median patient age is 65. Treatment following surgery relies on platinum chemotherapies which are nephrotoxic, ototoxic, and neurotoxic. This leads to the exclusion of up to 50% of the patient population effected by high-grade UC due to pre-existing conditions like decreased renal function or neuropathy. Monoclonal antibody therapies targeting the PD-1/PD-L1 relationship may be a more inclusive option for UC treatment.



Methods

A literature search was completed using PubMed and Google Scholar in November 2019 and six articles were selected for evaluation based on publishing date, relevance of the subject matter, and the study type for critical appraisal. Following selection, the study design of each article was evaluated.

Results

Safety

- Occurrence of high-grade AE was ≤16% in all of the immunotherapy groups
- High-grade AE in platinum-based chemotherapy controls ranged between 47% and 49.4%

Efficacy

- Objective response rate comparable or greater than chemo controls
- Statistically significant 6 and 12-month survival rates, rates greater than chemo control groups

Study	ORR	OS (months)	6 Mon. Survival	12 Mon. Survival	PFS (months)	High Grade AE (3-5)
Powles T et al. (2018) Atezolizumab	**High Exp:** Variable: 23% Control: 22% **Low Exp:** Variable: 13% Control: 13%	Variable: 11.1 Control: 10.6	N/A	Variable: 39.2% Control: 32.4%	Variable: 2.1 Control: 4.0	Variable: <10% Control: 47%
Patel et al. (2018) Avelumab	All: 17% High Exp: 24%	6.5	53%	N/A	1.4	<9%
Bellmunt et al. (2017) Pembrolizumab	Variable: 21.1% Control: 11.4%	Variable: 10.3 Control: 7.4	N/A	Variable: 43.9% Control: 30.7%	Variable: 2.1 Control: 3.3	Variable: 15.0% Control: 49.4%
Balar et al. (2017) Pembrolizumab	24%	N/A	67%	N/A	2.0	<16%
Powles T et al. (2017) Durvalumab	17.8%	All: 18.2 High Exp: 20.0 Low Exp: 8.1	64%	55%	1.5	6.8%
Balar et al. (2017) Atezolizumab	All: 23% High Exp: 28% Low Exp: 21%	15.9	N/A	57%	2.7	16%

Key: **Exp** – Expression of PD-L1; **ORR** – Objective Response Rate (Complete and Partial responses totaled); **OS** – Overall Survival; **PFS** – Progression Free Survival; **High Grade AE** - per National Cancer Institute Common Terminology Criteria for Adverse Events (AE)

Discussion

Six studies exploring four PD-1/PD-L1 targeting immunotherapies were analyzed and compared, assessing both the efficacy of the treatments and quality of the studies. Efficacy was determined using ORR, PFS, and 6 and 12-month survival rates in all studies. Controls were utilized in two of the six studies. Safety outcomes in all of the studies were determined by the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. These studies would be strengthened by utilizing greater blinding, randomization, and controls where not present. However, many of the studies were early clinical trials and the parameters of each study were strong enough to support the evidence presented.

Conclusion

The immunotherapy agents explored were found to be safe in a patient population that was determined to be ineligible for platinum chemotherapy for either comorbid conditions or disease progression while receiving treatment. All of the treatments examined were found to have much lower AE rates compared to typical chemotherapy. Additionally, survival rates were determined to be statistically significant. The main barrier to implementing these novel therapies is cost, as immunotherapy is significantly more expensive than chemo. Nonetheless, the combination of improved safety profiles and significant survival rates makes the utilization of PD-1/PD-L1 immunotherapies promising treatment options for high-grade UC.