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IMMUNOTHERAPY OF URINARY BLADDER CARCINOMA

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Summary

Urothelial urinary bladder carcinoma represents 9th most common malignancy in the world. This disease is held responsable for more than 165000 deaths throughout the world. In the past 30 years there were no major advances in treatment of this tumor. Chemotherapy regimens used for treatment are based on platinum compounds. In a recent time a series of immune system modulating drugs have been developed. This drugs have achieved excellent results in the treatment of urinary bladder carcinoma.

KEY WORDS**:** *urothelial carcinoma, immunotherapy, checkpoint inhibitors*

IMUNOTERAPIJA KARCINOMA MOKRAĆNOG MJEHURA

Sažetak

Karcinom mokraćnog mjehura je deveti najčešći maligni tumor u svijetu. Bolest je uzrok više od 165.000 smrtnih slučajeva. U posljednjih 30 godina nije bilo većih pomaka u mogućnostima liječenja ovoga tumora. Kemoterapijski protokoli za liječenje uznapredovale ili metastatske bolesti mokraćnog mjehura bazirani su uglavnom na spojevima platine. U posljednje vrijeme razvijen je niz novih lijekova koji moduliraju imunološki odgovor organizma na tumorske stanice i time omogućavaju uspješno liječenje karcinoma mokraćnog mjehura.

KLJUČNE RIJEČI**:** *karcinom mokraćnog mjehura, imunoterapija, checkpoint inhibitori*

INTRODUCTION

Urinary bladder urothelial carcinoma represents 9th most common malignancy in the world. This disease is held responsable for more than 165000 deaths worldwide (1). In the past 30 years there were no major advances in treatment of this tumor. Adjuvant treatment or treatment of advanced and metastatic disease is based on chemotherapy regimens containing platinum compounds in combination with other cytotoxic drugs (i.e. gemcitabin). Such regimens have limited efficacy, high toxicity and not every patient is able to have this kind of treatment due to higher median age of patients and comorbidities. Median overall survival rate after this chemotherapy regimens used as a first line of treatment is between 9 and 15 months.

In Croatia, urinary bladder carcinoma, is more common among male population with incidence od 757/100000 per year and mortality rate of 316/100000 yearly. This is the 5th most common malignancy in male population in Croatia. It is more rare in female population and it is not ranked in the first ten most common malignancies in female population (2).

Urothelial carcinoma is one of the first disease areas in which immunotherapy has been used. Intravesical application of BCG (Bacillus Calmette–Guérin) in non-muscle invasive disease has shown improvement in progression free survival.

Lately, a new class of drugs has been developed. These drugs are monoclonal antibodies belonging to the so-called checkpoint inhibitors class. The mechanism of action consits of selective binding of monoclonal antibodies to Programmed death-ligand 1 (PD-L1) expressed on the surface of some tumor cells, or to Programmed death-1 (PD 1) receptor expressed on the surface of activated T-cell. Blocking of one of these receptors checkpoint inhibition is blocked and T-cell is able to recognize, attack and destroy tumor cell.

Results of clinical studies with checkpoint inhibitors (atezolizumab, pembrolizumab, nivolumab, avelumab) have shown very good results and therefore some of this drugs are already approved in the USA and Europe and are included in clinical guidelines for the treatment of urothelial carcinoma.

Clinical trials

In clinical trials investigating the treatment of metastatic urothelial carcinoma checkpoint inhibitors were used as a second line treatment after the failure of first line platinum based chemotherapy. Atezolizumab, nivolumab, pembrolizumab and avelumab have shown efficacy in this setting.

Atezolizumab is an anti PD-L1 monoclonal antibody. It has been approved int he USA as a second line treatment of metastatic urothelial carcinoma by FDA (Food and Drug Administration) based on the results of phase II clincal trial called IMvigor 2010. The trial had two cohorts of patients with metastatic urothelial carcinoma with 429 patients enroled. First with no prior therapy and second with patients who received a first line chemotherapy based on platinum compund. Primary and point was overall response rate (ORR) and secondary endpoints progression free survival (PFS), overall survival (OS) and toxicity rate. The results in cohort previously treated with chemotherapy have shown median ORR of 16% and median OS of 6.9 months. In patients with Patients with highest expression of PD-L1 in tumor cells have achieved a median 12 month OS rate of 50% (3).

Nivolumab is an anti PD-1 monoclonal antibody approved by the FDA based on the data from phase II clinical trial Checkmate-257. In this trial, with 270 patients enroled, nivolumab has been used as a second line treatment for the patients suffering from locally advanced or metastatic urothelial carcinoma who have been treated with at least one line of chemotherapy . Primary endpoints have been ORR in all pts, ORR in pts with PD-L1 ≥ 5% or ≥ 1% and secondary endpoints PFS, OS, time to response (TTR),duration of response (DoR), safety, Quality of life (QoL). Results have shown an ORR of 19.6 months and median OS of 8.74 months. Longer median OS has been observed in patients with higher PD-1 expression reaching 11.3 months (4).

Pembrolizumab is also an anti PD-1 monoclonal antibody which has shown good results in second line treatment of locally advanced and metastatic urothelial carcinoma. A phase II clinical trial Keynote-045 compared the use of pembrolizumab with second line chemotherapy regimen (paclitaxel, docetaxel, vinflunine - investigator choice). Primary endpoints were OS, PFS and secondary endpoints were ORR, DoR. Median OS in arm treated wuth pembrolizumab has been 10.3 months and in chemotherapy arm 7.4 months (HR 0.73 ag 95%CI, p=0.0022) (5). This results show also a favorable effect of pembrolizumab use, and based on them the approval for use in second line treatment is imminent.

Avelumab is a programmed death ligand-1 (PD-L1) blocking monoclonal antibody. The drug has been approved by FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease progressed on or after platinum-based therapy or within 12 months of a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. The approval was based on data from the urothelial carcinoma cohorts of the single-arm, open-label JAVELIN Solid Tumor phase I trial, in which the overall response rate was 13.3% (95% CI, 9.1-18.4) among 226 patients who had been followed for at least 13 weeks, and was 16.1% (95% CI, 10.8-22.8) among 161 patients who had been followed for at least 6 months. In the ≥6-month follow-up cohort, the 26 responses included 9 (5.6%) complete responses (CRs) and 17 (10.6%) partial response (PRs). In the ≥13 weeks follow-up group, the 30 responses included 9 CRs (4%) and 21 PRs (9.3%). The median duration of response had not yet been reached for either arm and ranged from 1.4+ to 17.4+ months for both groups. The median time to response was 2 months (range, 1.3-11.0) for both groups. PD-L1 expression was evaluable in 84% of patients across

both cohorts. Among this population, there was no distinguishable variation in response rates based on tumor expression levels of PD-L1 (6).

CONCLUSION

Immunotherapy of urinary bladder cancer shows very interesting and promising results when used as a second line therapy for locally advanced and metastatic disease. It represents a great step forward in treatment of disease after a very long period. Although immunotherapy seems to be quite safe, secure and efficient, long term follow up should be conducted. We have to be aware of potential influence of the treatment to the stability of immune system and development of autoimmune diseases or even development of other kind of malignancies. In the light of good efficacy and acceptable toxicity rate the use of this drugs in first line treatment should be evaluated, and especially in patients not eligible for platinum based treatment.

REFERENCES

1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: A global overview and recent trends, Eu Urol, 2017, 96-108.
2. Hrvatski zavod za javno zdravstvo, Registar za rak Republike Hrvatske. Incidencija raka u Hrvatskoj 2014., Bilten 39, Zagreb 2016.
3. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial, Lancet. 2016;387: 1909-1920
4. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial, The Lancet Oncology, 2017; 3: 312-322.
5. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee Jy, Fong L, et al. KEYNOTE-045: Open-label, Phase 3 study of pembrolizumab vs investigator's choice of paclitaxel, docetaxel or vinflunine for previously treated advanced urothelial cancer. SITC (Clinical Immuno-Oncology Symposium) 2016.
6. Patel MR, Ellerton JA, Infante JR, Agrawal M, Gordon MS, Aljumaliy R, et. al. Avelumab in patients with metastatic urothelial carcinoma: Pooled results from two cohorts of the phase 1b JAVELIN Solid Tumor trial. Journal of Clinical Oncology 2017 35:6_suppl, 330-330.

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