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Experience of using pembrolizumab (“Keytruda”) in disseminated skin melanoma. Kazakhstan and Israel pilot study

Relevance. *Malignant neoplasms are one of the main causes of death in the Republic of Kazakhstan.*

The study was aimed to improve the metastatic skin melanoma treatment outcome. Tasks of the study: 1) To define exact effect of immunotherapy with Keytruda as PD1, PD2 inhibitor in disseminated skin melanoma. 2) To study the efficiency of immunotherapy in disseminated skin melanoma taking into account the biological characteristics of the tumour in the presence and absence of the BIRAF mutation.

Materials and methods. In 2016, the Kazakhstani part of Israeli-Kazakhstani pilot studies on a single protocol for the treatment of patients with metastatic skin melanoma using immunotherapy with pembrolizumab (Keytruda) have started in Almaty. 7 patients were recruited from Kazakhstan. They received 2 mg of Keytruda per 1 kg of weight per 100 ml of NaCl 0,9% i/v during 30 minutes, 3 injections each twenty-first day. Blood tests for LDH, S-100, CD4/CD8, genetic study of tumour for BIRAFV 600 mutation and PET were made before and after treatment.

Conclusion. The obtained experience showed high prospects of the studied type of immunotherapy in disseminated skin melanoma. The treatment was quite well tolerated by patients with no manifested side effects and gave a good chance for tumour stabilization and response.

Immunotherapy using Keytruda is more promising for patients with BIRAF-negative form of skin melanoma.

Keywords: melanoma, pembrolizumab (Keytruda), metastases, survival rate.

Actuality. Malignant neoplasms are one of the main causes of death in the Republic of Kazakhstan. Over the past 10 years, the cost of cancer in Kazakhstan has increased by 18 times. Unfortunately, quite a large proportion of patients are admitted to hospital with advanced stages of disease when standard methods of antitumor treatment are not very effective.

In 2015, Almaty hosted an international conference attended by the participants from Kazakhstan, Italy and Israel and devoted to immunotherapy using pembrolizumab (“Keytruda”, Merck Sharp & Dohme Corp.) and sodium nucleonate in disseminated skin melanoma and non-small cell lung cancer. Israeli oncologists reported their results of treatment by Keytruda. It was decided to conduct pilot joint studies according to a single protocol for patients with metastatic skin melanoma upon registration of Keytruda in Kazakhstan.

Materials and methods. In Kazakhstan, the pilot study was launched in 2016. The inclusion criteria were the morphologically verified diagnosis “metastatic form of skin and mucous melanoma” and the official refusal of the Multi-Disciplinary Group (MDG) of Cancer Centres to conduct antitumor treatment, as well as the absence of decompensated cardiovascular, pulmonary, renal, and hepatic insufficiency, and the availability of informed consent of the patient. 10 patients were recruited in Kazakhstan, without randomization.

Only 7 out of 10 recruited patients could receive the drug due to its high cost. The patients received 2 mg of Keytruda per 1 kg of weight per 100 ml of NaCl 0,9% i/v

during 30 minutes, 3 injections each twenty-first day. Blood tests for LDH, S-100, CD4 / CD8, genetic study of tumour for BIRAFV 600 mutation and PET were made before and after treatment.

Results. Out of 7 patients with metastatic skin melanoma receiving Keytruda, one patient with BIRAFV 600 positive mutation with brain metastases died from haemorrhagic stroke during the 1st year. Two patients with BIRAF negative form had a complete PET-confirmed tumour regression with a sharp, almost 3-fold decrease in LDH and S-100. 1 patient with BIRAFV 600 positive mutation had an increase of metastatic foci in regional lymph nodes during therapy with no PET-confirmed tumour progression and no significant changes in LDH and S-100 levels. Two patients with BIRAF negative form had a less than 50% reduction of tumour size. Patient monitoring is going on.

Conclusion. The data validity was low due to the small number of patients and a short period of observation. However, the obtained experience showed high prospects of the studied type of immunotherapy in disseminated BIRAF negative form of skin melanoma. The treatment was quite well tolerated by patients with no manifested side effects and gave a good chance for tumour stabilization and response.

We believe this therapy to be more promising in adjuvant mode in patients with high risk skin melanoma after surgical removal of metastases in regional lymph nodes. Further clarification requires a controlled multi-centre clinical trial.