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Research Article

Immune Homeostasis of Kidney Cancer

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Abstract

Kidney Cancer (KC) is the most aggressive disease with poor prognosis and bad results after chemotherapy and X-ray treatment. Immunotherapy has been recommended by ESMO since 2010. We have studied immune homeostasis of 13 patients with clear cell renal cell carcinoma: with local disease (n = 5), with regional disease (n = 4) and with metastases (n = 4). IH was examined 3-6 months after the surgery. We conclude that IH and clinical forms of KC were different. Metastatic KC has a high level of leucocytes and granulocytes, depletion of CD 16 and cytokines reactivity is considerably reduced due to IL-2 and IFN-γ.

Keywords: *Kidney Cancer (KC); Immune Homeostasis (IH); cytokines*

Abbreviations: KC - Kidney Cancer; IH - Immune Homeostasis; CT – Computed Tomography;MRI – Magnetic Resonance Imaging; Cr – Coefficient of Reactivity; CI - Confidence Interval.

Introduction

In the structure of oncologic diseases, KC is 2-3%, with the highest rates observed in the Western European countries. The main histological form of KC is clear cell renal cell carcinoma (this type accounts for about 70-80%). [2,5] The overall increasing trend in incidence in recent years is related to widespread introduction of modern diagnostic techniques Ultrasound, CT, MRI – which allow to diagnose asymptomatic forms of the disease. [8,9] KC remains a tumor with low rates of 5 year survival. Renal cell carcinoma does not generally respond to chemotherapy or radiation. [1,6]

Targeted immunotherapy is in a stage of scientific development and has no wide application. [3,7,10] According to ESMO Guidelines, basic adjuvant therapy for clear cell renal cell carcinoma is immunotherapy with cytokines. [6] Some researchers believe that the use of cytokines can help only for the prediction of response to therapy, because local growth of the tumor and systemic immune response are not identical. It's necessary to know the correspondence between the stage of the disease and the degree of disruption of immune homeostasis (IH). [4]

The aim of this paper is to evaluate the immune homeostasis with different clinical forms of distribution of KC in order to justify the individual treatment schemes with cytokines.

Materials and Methods

From 2010 to 2014, 13 patients with clear cell renal cell carcinoma of the USMU department of oncology were included in the research, the age of the patients is 56, 7 ± 6,9 (mean follow-up time is 2,6 years). All patients were divided into three groups: with local disease (stage 1a-2a, n = 5), with regional disease (stage 1b-2b, n = 4) and metastatic KC (M1, n = 4). IH was assessed 3-6 months after radical resection of the kidney/ nephrectomy, or 1-2 months after diagnosis of inoperable tumor and starting palliative therapy. (We have studied the indicators of hemogramm). The study was based on the indicators of hemogram: the level of leukocytes, lymphocytes, granulocytes,

platelets and hemoglobin; the indicators of immunogram: $CD3^+$, $CD4^+$, $CD8^+$, CD16 T-cells, CD20 B-cells; and inflammatory cytokines (IL-2, IFN-γ, TNF-α). The range of reaction was Cr index (Cr=n$CD3^+$ stimulation/n$CD3^+$ wild where n= $CD3^+$ count which can synthesize cytokines TNF-α, IL-2, IFN-γ in the tests after stimulation and in wild) with 95% confidence interval (CI) and index t, p. [4,11,12].

Results and Discussion

Table 1 provides the average indicators of hemogram, immunogram, inflammatory cytokines and the range of Cr reaction with 95% confidence interval (CI) in study groups. The groups of patients with regional KC had no significant differences of immunogram indicators.

The table 1 compares indicators of immunograms in patients with kidney cancer in study groups.

Parameters/ unit of measure	Hemogram					
	1 Group	95% CI	2 Group	95% CI	3 Group	95% CI
Leu/10^9l	5,8 ± 1,7*	3,8-7,8	7,0 ± 2,3	3,8-10,2	8,6 ± 0,9*	7,2-9,9
Lymph/10^9l	1,9 ± 0,4	1,4-2,3	1,9 ± 0,4	1,2-2,8	1,8 ± 0,48	1,2-2,6
Granulocytes /10^9l	3,4 ± 1,5*	1,7-5,1	3,7 ± 1,4*	1,1-6,2	6,1 ± 1,03*	4,6-7,5
Hemoglobin/ g/l	129 ± 13,9	113-145	127 ± 25,4	91,7-162,3	130,5 ± 25,5	95,1-165,9
Platelets/10^9l	240 ± 52,8	179-300	230,3 ± 62,8	143,1-317,4	394,3 ± 158,8	173,8-614,7
Erythrocytes/ 10^{12}l	4,4 ± 0,4	3,9-4,9	4,7 ± 0,7	3,7-5,7	4,8 ± 0,3	4,4-5,2
Immunogram						
CD3+/10^9l	1,4 ± 0,2	1,0-1,7	1,2 ± 0,24	0,78-1,7	1,3 ± 0,3	0,86-1,8
CD4+/10^9l	0,8 ± 0,1	0,67-1,0	0,7 ± 0,2	0,37-1,1	0,7 ± 0,1	0,56-0,9
CD8+/10^9l	0,5 ± 0,2	0,18-0,75	0,4 ± 0,18	0,09-0,75	0,5 ± 0,4	0,03-1,02
CD16/10^9l	0,32 ± 0,09	0,18-0,44	0,5 ± 0,33	0,01-1,12	0,29 ± 0,14	-0,11-0,48
CD20/10^9l	0,3 ± 0,16	0,07-0,5	0,2 ± 0,07	0,08-0,34	0,18 ± 0,01	0,16-0,19
Cytokines						
TNF-α/% w	0,44 ± 0,1	0,31-0,57	0,85 ± 0,35	-0,2-1,9	1,0 ± 1,4	-1,04-3,04
«Cr» TNF-α	85,9 ± 48,4	30,3-41,7	40,7 ± 22,4	-27,7-109,2	109,6 ± 119,2	-55,9-275,1
IL-2% w	0,5 ± 0,3*	0,15-0,84	0,5 ± 0,4	0,7-1,8	0,1 ± 0,08*	-0,01-0,21
«Cr», IL-2	53,5 ± 41,1	6,5-100,6	69,8 ± 82,4	-180,8 ± 320,4	10177 ± 20148	-17793-38147,9
IFN-γ % w	0,14 ± 0,05*	0,07-0,2	0,15 ± 0,07	-0,06 ± 0,37	0,05 ± 0,06	-0,02 ± 0,12
«Cr» IFN-γ	96,8 ± 119,2	40,2-33,8	181,0 ± 199,4	425,6-787,7	8662,7 ± 0067,3	-5312,9-22638,5

Note: **p – statistical reliability ≤ 0,05*

*** p – statistical reliability ≥ 0,05 u ≤ 0,09 (trend).*

Table 1: *compares indicators of immunograms in patients with kidney cancer in study groups.*

The hemogram indicators are reliable for the local disease and the metastasis KC groups for absolute leucocytes and granulocytes count. The twofold increase of granulocytes in patients with metastases is a factor of poor outcome which is typical for generalization. The patients of group 2 had mixed parameters of granulocytes count which is typical for patients of group 1 and 3. It may be connected with the manifestation of latent metastases. The depletion of CD 16 for all groups is a sign of the depletion of absolute NK count. Only local KC maintains function of $CD3^+$ T-cells which can synthesize cytokines IL-2 and IFN-γ. In groups 2 and 3, there is an increase in the range of activity of the pro-inflammatory cytokines, in particular, IL-2 and IFN-γ.

Conclusion

We conclude that IH and clinical forms of KC were different. KC in group 1 shows norm reaction of pro-inflammatory cytokines IL-2 and IFN-γ. KC in group 3 reveals the depletion in activity of the pro-inflammatory cytokines IL-2 and IFN-γ. The examination of group 2 of patients is the most informative. This group has diverse immunological parameters which require high-quality diagnostics of latent metastases and individual selection of cytokine therapy. The results provided are consistent with the findings from the first clinical and immunological conference on Oncology in Europe in 2014.

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Conflict of interest

The authors declare no conflicts of interest.

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