

УРОВНИ МЕСТНЫХ ЦИТОКИНОВ КАК ПРОГНОСТИЧЕСКИЙ ФАКТОР РАННЕГО РЕЦИДИВА НЕМЫШЕЧНО- ИНВАЗИВНОЙ КАРЦИНОМЫ МОЧЕВОГО ПУЗЫРЯ

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Резюме. Цель работы – дать оценку локального уровня цитокинов в качестве возможных прогностических факторов раннего рецидивирования немышечно-инвазивного мочевого пузыря (НМИРМП). В исследование включено 75 больных: 51 с первичным и 24 – с рецидивным НМИРМП; в обеих группах были опухоли высокой и низкой степени злокачественности (HG и LG). Больных с первичным НМИРМП наблюдали в течение 9 мес. после лечения: ТУР и адьювантная химиотерапия (№6). Из образцов опухолевой ткани готовили супернатанты, в которых определяли уровни цитокинов (IL-1 β , IL-6, IL-10, IL-18, TNF α , IFN γ , IL-8) методом ИФА. Результаты исследования показали, что у больных с первичным НМИРМП рецидивы развились в 15 случаях (46,8%) LG и в 11 (45%) – HG-опухолей; не выявлено различий в зависимости от степени злокачественности. В исходно рецидивных опухолях как HG, так и LG, уровни цитокинов были максимальными: в LG они превышали первичные от 7,1 (IFN γ) до 300 (IL-6) раз, в HG – от 2,0 (IL-10) до 9,7 (IL-6) раз. Уровни IL-1 β , IL-6, IL-10, IFN γ , IL-8 были выше в тех первичных LG-опухолях, которые рецидивировали через 6-9 мес. наблюдения, чем в нерецидивировавших, хотя их содержание было значительно ниже, чем в исходно рецидивных опухолях (от 2,6 раз для IFN γ до 150 раз для IL-6). Сходная тенденция, хотя и не по тем же цитокинам, наблюдалась в HG-опухолях: тканевые уровни IL-6, IL-10, IL-18 и TNF α были выше в опухолях, рецидивировавших через 6-9 мес. после лечения. Повышение уровней двух цитокинов было общим для LG- и HG-опухолей (IL-6 и IL-10), что можно рассматривать в качестве нового фактора

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негативного прогноза. Таким образом, рецидивирование LG и HG НМИРМП связано с некоторыми иммунологическими механизмами, а именно с локальной гиперпродукцией цитокинов, особенно IL-6 и IL-10, хотя IL-1 β , IL-8, IFN γ могут играть роль при LG, а IL-18, TNF α – при HG-опухолях. Учитывая общие сигнальные пути IL-6 и IL-10 (JAK/STAT), эти транскрипционные факторы могут быть потенциальными мишенями для новых эффективных подходов к лечению.

Ключевые слова: цитокины, микроокружение опухоли, прогноз, немышечно-инвазивный рак мочевого пузыря, раннее рецидивирование

LOCAL CYTOKINE LEVELS AS PROGNOSTIC FACTORS FOR EARLY RELAPSE OF NON-MUSCLE-INVASIVE BLADDER CARCINOMA

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Abstract. The aim of our study is to assess the local cytokine levels as prognostic factors for early relapse in NMIBC patients. 75 patients with NMIBC were enrolled in the study: 51 with primary NMIBC and 24 with initially recurrent NMIBC, LG and HG tumors were diagnosed in each group. Patients with primary NMIBC were monitored during 9 months after treatment: TURB and chemotherapy (No. 6). During TURB samples of tumors were taken, supernatants were obtained and tissue cytokine levels were measured (IL-1 β , IL-6, IL-10, IL-18, TNF α , IFN γ , IL-8) by ELISA test. The results showed that in patients with primary NMIBC early relapses were diagnosed in 15 (46.8%) of LG tumors and in 11 (45%) of HG tumors matching that there was no difference depending upon tumor grade. In initially recurrent tumors of both LG and HG NMIBC the amounts of cytokines were maximal: in LG tumors they exceeded the primary ones from 7.1 (IFN γ) to 300 (IL-6) while in HG – from 2.0 (IL-10) to 9.7 (IL-6). The amounts of IL-1 β , IL-6, IL-10, IFN γ , IL-8 were higher in those LG primary tumors which relapsed in 6-9 months compared to the ones which didn't, though their levels were much lower than in initially manifested relapse (from 2.6 times for IFN γ to 150 times for IL-6). A similar trend, though not for all the same cytokines, was observed in HG tumors: tissue levels of IL-6, IL-10, IL-18 and TNF α were higher in tumors which relapsed in 6-9 months after treatment. The increase of 2 cytokines' levels were common for both LG and HG tumors (IL-6 and IL-10). This finding might be considered as a new prognostic factor of the early relapse. We conclude that relapse of LG and HG NMIBC is related to some immune mechanisms, namely to local hyperproduction of cytokines, especially IL-6 and IL-10, though IL-1 β , IL-8, IFN γ could have an impact on LG and IL-18, TNF α – on HG tumors. Taking into account common signaling pathways of IL-6 and IL-10 like JAK/STAT, these transcription factors might be potential targets for new effective approaches to treatment.

Keywords: cytokines, tumor microenvironment, prognosis, non-muscle-invasive bladder carcinoma, early relapse

Introduction

Chronic inflammation is considered to be one of the main triggers of carcinogenesis in many types of malignant tumors. Local hyperproduction of cytokines by tumor cells or activated macro-

phages and lymphocytes contributes to tumor microenvironment (TME) formation which plays a crucial role in immunoediting of tumor growth [3, 6, 12]. It is well known that cytokines are able to enhance neoangiogenesis and epithelial-mesenchymal transition (EMT), and disrupt

the extracellular matrix, as well as to cause the migration to TME of immunosuppressive cells like M2, Tregs or MDSC [13]. Inflammatory cytokines can cause epigenetic modifications that upregulate the expression of oncogenes or downregulate the expression of tumor-suppressor genes [5]. IL-10, IL-6, TGF- β are described by many researchers as prooncogenic, nevertheless cytokines, proclaimed as immunostimulating (IL-1 β , TNF α , IFN α and γ and some others) seem to possess dual function in tumor-bearing organism and demonstrate promotion not only of immune response but also of tumor growth [8].

Relapse of malignant tumors following months or even years after treatment including surgery and radio- and/or chemotherapy is usually considered to be a problem of insufficiently radical approach. But nowadays more and more data proves the biologic causes of tumor recurrence, emphasizing the role of cancer stem cells [9] and cytokines of TME [7, 10]. At the time of the first referring for medical care 75-80% of patients with urothelial bladder carcinoma have non-muscle-invasive tumor (NMIBC), i.e. located in mucosa (Ta, CIS), or submucosa (st. T1). Though it is the initial stage of bladder cancer, the tumor has a marked tendency to recur even when the treatment is started timely.

According to European Organization for the Research and Treatment of Cancer (EORTC) the most often type of tumor progression in NMIBC is relapse occurring in 37% of patients with low risk, in 65% of patients with intermediate risk and in 84% of patients with high risk after transurethral bladder resection (TURB) and adjuvant chemotherapy. In the last case early relapses are typically diagnosed during 6-12 months after surgery and chemotherapy, especially in high grade (HG) carcinomas; such patients need more aggressive treatment. That is why the search for new prognostic factors which might also serve as targets for treatment of NMIBC is an topical medical and biological problem.

The aim of our study is to assess the local cytokine levels as prognostic factors for early relapse in NMIBC patients.

Materials and methods

Seventy-five patients with NMIBC were treated in the Department of Urology of National Medical Research Centre for Oncology, Rostov-on-Don, Russia. The group of 51 patients (46 men (90.2%) and 5 women (9.8%) aged 40-83 years) had primary NMIBC which was histologically verified as papillary urothelial carcinoma: low grade (LG, n = 31 or 60.8%) and high grade (HG, n = 20 or 39.2%). All the patients were in high and intermediate risk groups according to EORTC; they received surgical treatment (TURB) and 6 courses of adjuvant intravesical chemotherapy. Patients were monitored during 9

months after treatment. Patients of the group with initially recurrent NMIBC (n = 24), had LG tumors (n = 15 or 62.5%) and HG tumors (n = 9 or 37.5%). They were also subjected to surgical treatment and chemotherapy according to the accepted standards. Prior to enrollment in the study, all participants gave written informed consent.

The samples of tumors were taken from all the patients during TURB, disintegrated by BD Medimachine (USA), supernatants were obtained by centrifugation and stored at -80 °C. After thawing sandwich Elisa test was performed with cytokine kits to estimate the levels of IL-1 β , IL-6, IL-10, IL-18, TNF α , IFN γ , IL-8 (Vector-Best, Russia) by Uniplan Reader (Russia). Total protein amount was measured by biuret test on analyzer Sinnowa Medical Science and Technology Co (China). Cytokine levels were expressed in pg/mL per 1 g protein. Statistical analysis was performed by program STATISTICA 13 (StatSoft Inc., USA). Since our data had no Gaussian (normal) distribution they were represented as median with interquartile range, 25 and 75 percentiles – Me (Q_{0.25}-Q_{0.75}). Intergroup differences were estimated by Mann-Whitney U test. Statistically significant differences were accounted when p < 0.05.

Results and discussion

During the period of clinical monitoring of the patients with primary NMIBC early relapses were diagnosed in 15 (46.8%) of them with LG tumors and in 11 (45%) with HG tumors matching that there was no difference depending upon tumor grade. Patients without these early relapses were regarded as groups 1 in LG and 4 in HG (better prognosis) and with newly diagnosed early relapses as groups 2 in LG and 5 in HG (worse prognosis) while patients with initially recurrent tumors formed groups 3 in LG and 6 in HG.

Comparative analysis of tissue cytokine contents between these groups with different course of the disease is shown in Table 1. In relapse tumors (groups 3 and 6) of both LG and HG NMIBC the amounts of most of cytokines were maximal: in LG tumors they exceeded the primary ones from 7.1 (IFN γ) to 300 (IL-6) while in HG – from 2.0 (IL-10) to 9.7 (IL-6). It is worth noting that in HG tumors some cytokines demonstrated no difference between the recurrent and the primary ones (IFN γ) and IL-18 level was higher in relapse HG tumors than in primary ones of the group 4, but not 5.

We found out that primary tumors which manifested relapse after 6-9 months after treatment also contained higher cytokine levels than primary tumors without relapse during this period and it was typical for both groups. The amounts of IL-1 β , IL-6, IL-10, IFN γ , IL-8 were statistically significantly higher in those LG primary tumors which relapsed in 6-9 months compared to the ones which didn't,

TABLE 1. TISSUE CYTOKINE LEVELS IN TUMORS OF NMIBC PATIENTS WITH DIFFERENT COURSE OF THE DISEASE, Me (Q_{0.25}-Q_{0.75})

Cytokine level (pg/mL per 1 g of protein)	Groups of patients							
	NMIBC LG				NMIBC HG			
	1 Primary without relapse, n = 16	2 Primary with relapse in 6-9 months, n = 15	3 Relapse, n = 15	p	4 Primary without relapse, n = 11	5 Primary with relapse in 6-9 months, n = 9	6 Relapse, n = 9	p
IL-1 β	13.3 (10.2-17.9)	19.8 ¹ (19.1-48.9)	149.2 ^{1,2} (83.0-215.4)	p ₂₋₁ = 0.038 p ₃₋₁ = 0.001 p ₃₋₂ = 0.001	31.3 ¹ (17.3-41.0)	38.5 ² (26.7-49.6)	83.8 ^{3,4,5} (60.8-91.1)	p ₆₋₄ = 0.035 p ₆₋₅ = 0.04
IL-6	1.1 (0.6-1.5)	2.6 ¹ (2.2-7.3)	330.2 ^{1,2} (167.8-492.6)	p ₂₋₁ = 0.025 p ₃₋₁ = 0.001 p ₃₋₂ = 0.001	3.0 ¹ (1.3-3.9)	6.2 ^{2,4} (4.5-9.2)	29.2 ^{3,4,5} (29.1-31.7)	p ₅₋₄ = 0.027 p ₆₋₄ = 0.011 p ₆₋₅ = 0.008
IL-10	3.2 (2.1-4.2)	5.9 ¹ (4.9-9.9)	55.4 ^{1,2} (29.4-81.4)	p ₂₋₁ = 0.039 p ₃₋₁ = 0.012 p ₃₋₂ = 0.019	3.6 (1.6-3.9)	5.1 ⁴ (4.2-5.6)	7.2 ^{3,4,5} (6.1-10.5)	p ₅₋₄ = 0.04 p ₆₋₄ = 0.039 p ₆₋₅ = 0.037
IL-18	59.7 (41.8-90.0)	57.3 (31.7-81.5)	641.0 ^{1,2} (478.2-903.9)	p ₃₋₁ = 0.014 p ₃₋₂ = 0.016	22.8 ¹ (20.3-34.4)	87.6 ^{2,4} (83.9-124.1)	69.0 ^{3,4,5} (46.9-80.4)	p ₅₋₄ = 0.012 p ₆₋₄ = 0.001 p ₆₋₅ = 0.035
TNF α	10.1 (5.9-13.8)	10.0 (7.1-17.5)	212.0 ^{1,2} (113.3-310.7)	p ₃₋₁ = 0.001 p ₃₋₂ = 0.001	5.5 ¹ (4.5-7.2)	10.9 ⁴ (8.3-12.7)	22.7 ^{3,4,5} (21.9-42.7)	p ₅₋₄ = 0.032 p ₆₋₄ = 0.018 p ₆₋₅ = 0.012
IFN γ	6.9 (4.9-8.4)	19.0 ¹ (11.1-38.9)	49.0 ^{1,2} (28.9-69.2)	p ₂₋₁ = 0.021 p ₃₋₁ = 0.017 p ₃₋₂ = 0.039	15.2 ¹ (11.0-20.9)	11.2 (5.3-19.4)	10.8 ³ (9.8-16.1)	
IL-8	13.0 (8.4-15.3)	26.4 ¹ (22.4-37.8)	663.4 ^{1,2} (341.6-985.2)	p ₂₋₁ = 0.028 p ₃₋₁ = 0.001 p ₃₋₂ = 0.001	69.4 ¹ (47.5-113.2)	42.6 ^{2,4} (38.4-45.7)	190.9 ^{3,4,5} (125.7-329.2)	p ₅₋₄ = 0.043 p ₆₋₄ = 0.014 p ₆₋₅ = 0.022

though their levels were much lower than in initially manifested relapse (2,6 times for IFN γ and 150 times for IL-6). A similar trend, though not for all the same cytokines, was observed in HG tumors: tissue levels of IL-6, IL-10, IL-18 and TNF α were statistically significantly higher in tumors which relapsed in 6-9 months after treatment. This finding might be considered a new prognostic factor of the early relapse. Based on the values of the ranged data represented as LQ and UQ we tried to specify the limits of cytokines' indicators possibly prognostic for early relapse during the period of monitoring. For LG tumors the value appeared to be IL-1 β > 18.0, IL-6 > 1.5, IL-10 > 4.2, IFN γ > 8.4, IL-8 > 15.3 pg/mL per 1 g of protein and for HG tumors IL-6 > 3.9, IL-10 > 3.9, IL-18 > 34.4,

TNF α > 7.2 pg/mL per 1 g of protein. We observed that the increase of 2 cytokines' levels were common for both LG and HG tumors (IL-6 and IL-10). So they might be used as a possible prognostic factors for early relapse in patients with NMIBC though verification on more broad groups and more prolonged monitoring is needed.

Accounting the biologic properties of both cytokines, it is rather expected. IL-6 induces invasion and metastasis through the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway and thus is able to activate a wide array of signaling pathways and transcription factors promoting EMT, fostering the acquisition of mesenchymal features in cancer cells [1]. The other type of its'

proneogenic activity is support of cancer stem cells which are considered to be a pool for relapse forming from treatment-resistant tumor cells [11].

IL-10 is known to be an immunosuppressive factor of TME due to suppression of T cell proliferation, modulation of APCs, preservation of the activity/stability of Treg cells, though it remains unclear if it can stimulate them [4]. Notably, both IL-6 and IL-10 are involved in STAT3 activation matching that pro-inflammatory and anti-inflammatory cytokines can work through the same signaling pathway, although they perform very distinct functions and their downstream mechanisms are different. In the review cited above the authors point out that in macrophages, both IL-10 and IL-6 induce the activation of SOCS3, and this could be the target for future therapeutic approaches.

From our previous experience, high levels of IL-6 and IL-10 in TME were factors of poor prognosis in patients with melanoma and esophageal carcinoma [2, 14, 15].

Conclusions

We consider that relapse of LG and HG NMIBC is related to some immune mechanisms, namely to local hyperproduction of cytokines, especially IL-6 and IL-10, though IL-1 β , IL-8, IFN γ could have an impact on LG and IL-18, TNF α – on HG tumors. Taking into account common signaling pathways of IL-6 and IL-10 like JAK/STAT, these transcription factors might be potential targets for new effective approaches to treatment.

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