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PREDICTIVE ROLE OF CD4⁺ T-LYMPHOCYTES IN TREATMENT RESPONSE OF SOFT TISSUE SARCOMAS

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Abstract

This study highlights the particular importance of CD4 T-lymphocyte levels in the immune microenvironment of soft tissue sarcomas. Data analysis shows that high levels of active CD4⁺ T-lymphocytes inside the tumor are associated with more favorable morphological responses to therapy, as well as improved clinical outcomes. CD4 levels serve as a promising prognostic marker and can contribute to more accurate prediction of the results of complex treatment, including immunotherapy. The obtained results emphasize the need for expanded research to develop new individualized strategies to enhance the immune response and improve the effectiveness of soft tissue sarcoma therapy.

Keywords: *soft tissue sarcoma, tumor microenvironment, chemotherapy, radiation therapy*

Introduction

The relevance of the study is due to the high heterogeneous nature of soft tissue sarcomas and their complexity in diagnosis and treatment, which is confirmed by numerous international studies. According to modern data, soft tissue sarcomas constitute about 1% of all malignant tumors and are characterized by a high degree of morphological and molecular diversity, which complicates not only the diagnosis but also the selection of optimal therapy (Huang H., Fan Y., Zhang S., Bai X., Wang X., Shan F., 2025). These tumors are characterized by high aggressiveness, a high risk of recurrence, and low patient survival rates, especially in advanced stages of the disease. In the context of modern trends in global oncology, the role of the tumor's immune microenvironment and its components, primarily the activity of T-lymphocytes with the CD4 marker, which perform regulatory and supporting functions in the antitumor immune response, is gaining particular importance. International studies show that the presence of active CD4⁺ T-lymphocytes within the tumor tissue is associated with improved prognosis, reduced metastasis risk, and higher tumor sensitivity to immunotherapeutic approaches (Van der Graaf W.T.A., Orbach D., Judson I. R., Ferrari A., 2017).

An additional factor is that the activity of CD4⁺ cells contributes to the activation of

cytotoxic T-lymphocytes and macrophages, increased cytokine synthesis, and the development of an immunological microenvironment favorable for the elimination of tumor cells. In light of the rapid implementation of immunotherapy as an innovative method in oncological practice, understanding the role of $CD4^+$ T-lymphocytes as a prognostic and predictive marker is becoming particularly relevant. The introduction of an assessment of the immune status, in particular the level of CD4, can contribute to a more accurate prediction of treatment outcomes, the selection of personalized therapeutic regimens, and the development of new combined methods that enhance the antitumor immune response (Lee A. Q., Hao C., Pan M., Ganjoo K. N., Bui N., 2024).

Thus, the study and assessment of the role of CD4-lymphocytes in the microenvironment of soft tissue sarcomas is a crucial area contributing to increased treatment efficacy, reduced risk of relapses, and increased life expectancy. These tasks correspond to the current global trends in the development of oncology and require further scientific research to confirm and implement them in clinical practice (Wood G. E., Meyer C., Petitprez F., D'Angelo S.P., 2024; Recine F., Vanni S., Bongiovanni A., Fausti V., Mercatali.L, Miserocchi G., et al., 2024).

Materials and methods

The study was conducted at the Children's Oncology, Hematology and Immunology Scientific and Practical Medical Center, as well as the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology and its Tashkent City Branch, in the period from 2014 to 2024. 174 patients diagnosed with rhabdomyosarcoma of various localizations participated in the study.

Inclusion criteria: diagnosis of soft tissue sarcoma, availability of data on chemotherapy and material for immunohistochemical analysis. Patients with preliminary immunotherapy or insufficient volume of biopsy material were excluded.

To assess the immune microenvironment, tumor tissue samples obtained by biopsy were used. The samples were fixed in 10% formalin and enclosed in paraffin. 4 μm thick sectional cuts were stained using antibodies to determine the status of CD4, CD8, CD20, and CD68. The results of the pathohistological examination were evaluated by two independent pathologists. Assessment of the location of immune cell infiltration was carried out by dividing the samples into intratumoral and peritumoral zones. Cell counting was performed in 5 independent fields of view using microscopy. The results were recorded as the percentage of positive cells from the total number of cells in the visual field.

To analyze the differences in the level of infiltration and response to chemotherapy, Pearson's chi square and Fisher's precision criteria were used. The significance level was established at $p<0.05$. All calculations were carried out using statistical software.

This approach provided a detailed assessment of the immune microenvironment and its impact on clinical outcomes in patients with soft tissue sarcomas.

Results

An analysis of the therapy effectiveness was conducted depending on the CD4 status.

Table 1. *Analysis of therapy effectiveness depending on CD 4 status*

Indicators	Category	CD 4 Status		p
		negative status	positive status	
Chemotherapy effect (complete-1, partial-2, stabilization-3, progression-4)	Full effect	7 (10.0)	15 (17.2)	0.320
	Partial effect	28 (40.0)	37 (42.5)	
	Stabilization	32 (45.7)	29 (33.3)	
	Progression	3 (4.3)	6 (6.9)	
Degree of therapeutic pathomorphosis	therapeutic pathomorphosis I	21 (30.0)	11 (12.6)	0.002*

Indicators	Category	CD 4 Status		p
		negative status	positive status	
Radiation therapy response	therapeutic pathomorphosis II	31 (44.3)	28 (32.2)	0.253
	therapeutic pathomorphosis III	10 (14.3)	26 (29.9)	
	therapeutic pathomorphosis IV	8 (11.4)	22 (25.3)	
	Full effect	6 (15.8)	12 (16.9)	
	Partial effect	20 (52.6)	25 (35.2)	
	Stabilization	6 (15.8)	22 (31.0)	
	Progression	6 (15.8)	12 (16.9)	

** – differences in indicators are statistically significant ($p < 0.05$)*

Analysis of the presented data shows that there is a statistically significant correlation ($p = 0.002$) between the status of CD4 and the effectiveness of therapy, in particular, the degree of therapeutic pathomorphosis. This indicates that the presence of a positive CD4 status (presence of active T-lymphocyte helpers) contributes to more pronounced morphological regression of the tumor and, possibly, a more effective response to the ongoing treatment. Positive CD4 status apparently reflects the body's more active immune response, which contributes to a decrease in tumor mass and an increase in therapeutic effect.

At the same time, the influence of the CD4 status on the clinical response, measured by signs of complete, partial, stabilizing effect and progression, was not revealed, since no statistically significant differences in this indicator ($p = 0.320$) were recorded. This indicates that macroscopic effectiveness and morphological pathomorphism can be more sensitive to the immune status than the clinical response in terms of symptomatic or hormonal improvement.

Theoretically, a positive CD4 status contributes to the enhancement of phagocytic and stimulatory functions of immune cells, activates the cytokine mechanism, promotes the development of anti-tumor T-lymphocytes, which together enhances the anti-tumor immune response. This promotes more pronounced regression of tumor tissues under the influence of treatment, including radiation therapy. At the same time, the absence of significant differences in the effects of radiation therapy in different CD4 states can be explained by the fact that the immune system plays a role more as an auxiliary component in the context of radiation therapy, while the main effect is due to radiation load.

Summarizing, it can be said that the presence of a positive CD4 status is an important biological factor predisposing to more effective morphological regression of the tumor, which confirms the active role of the immune mechanism in the treatment of sarcomas. These data indicate the need for further research to clarify the precise mechanisms of interaction between immune cells and radiotherapy and to find immunological markers capable of predicting treatment outcomes and developing new approaches to immunoradiotherapy.

Conclusion

The presence of a positive CD4 status is associated with more pronounced morphological regression of the tumor and a high level of therapeutic pathomorphosis, which indicates the important role of T-helper lymphocytes in enhancing the anti-tumor effect in the treatment of soft tissue sarcomas. However, the influence of CD4 status on the clinical response (complete, partial, stabilization, progression) has not been established, which may indicate more complex mechanisms of immune system interaction and treatment effectiveness. These

data indicate the need for further research to understand the role of immune cells and their potential in predicting and improving sarcoma therapy.

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Kahharov A.J. – assistance in text correction

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