

CORRECTION OF IMMUNOSUPPRESSION IN CANCER PATIENTS DEPENDING ON THE TYPE OF ANESTHESIA

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Resume. The conducted comparative assessment of the effectiveness of the proposed treatment and diagnostic algorithm for the correction of perioperative immunosuppression in cancer patients showed its high clinical effectiveness. The use of immunocorrection before surgery provided a significant improvement in the indices of both cellular and humoral immune responses, with a limitation of the severity of the inflammatory cascade, a decrease in the level of proinflammatory cytokines and stabilization of the activity of regulatory links.

Key words: immunosuppression, immunocorrection, immunity, anesthesia.

Relevance. The problem of perioperative immunosuppression in cancer patients has been actively discussed in the scientific literature since the end of the 20th century, when it became obvious that surgical intervention, despite the radicality of tumor removal, is often accompanied by an increased risk of metastasis. Works of this period established that the tissue trauma itself, accompanying the operation, causes activation of the neuroendocrine stress axis and subsequent systemic immunosuppression (1,3,5). Several studies have shown that the use of epidural or spinal anesthesia can reduce the level of systemic inflammation by reducing the release of catecholamines and cortisol, thereby preserving the antitumor activity of the immune system (7,9). Meanwhile, despite the results obtained, the question of the effect of different anesthetic methods on long-term patient survival remains open (1,2,4).

Data on the advantage of one type of anesthesia over another remain contradictory, since studies differ significantly in design, tumor type, and patient characteristics (6,8). Such data open new prospects for pharmacological correction of disorders.

The aim of the study is to develop a treatment and diagnostic algorithm for the correction of perioperative immunosuppression in cancer patients depending on anesthetic care.

Materials and methods. The study included 120 oncological patients subject to planned surgical treatment for malignant neoplasms of various anatomical locations

for the period from 2021 to 2025 in the Bukhara regional branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology.

Thus, the distribution by the type of anesthetic intervention was completely balanced and ensured the methodological purity of the comparison of immunological parameters both between and within groups.

For an objective quantitative assessment of the results of immunosuppression correction in oncological patients who underwent surgery, this study used the original unified scale for clinical assessment of the effectiveness of anesthetic care, developed within the framework of this methodological recommendation.

The scale is a structured tool consisting of six independent clinical and functional criteria reflecting the key aspects of the early postoperative period. A three-level assessment system is applied to each criterion: "good" (4 points), "satisfactory" (2 points), and "unsatisfactory" (0 points).

The following parameters were selected for assessment: 1) hemodynamic stability, 2) need for analgesia, 3) awakening characteristics, 4) presence and severity of side effects, 5) need for postoperative observation in the intensive care unit, 6) rate of early recovery of functional activity.

Each criterion was recorded during the first 72 hours after surgery and assessed by a commission of the attending physician, anesthesiologist, and applicant. The total score on the scale could range from 0 to 24. In accordance with the established thresholds, the obtained results were interpreted as follows: ≥ 20 points - clinically highly effective (excellent) anesthetic care; 12-18 points - satisfactory (acceptable); < 12 points - unsatisfactory (questionable from the point of view of clinical validity).

Results and discussion. The first stage of developing the diagnostic scale of immunological admissibility was the correlation analysis between the key parameters of the cellular link of the immune system in cancer patients. The overall profile of the obtained matrix demonstrates moderate mutual independence of most parameters. In particular, the CD3⁺ level did not demonstrate significant correlations with other indicators (maximum value $\rho=0.093$ with CD8⁺), which reflects its limited discriminatory value as a marker of functional differentiation. CD8⁺ T-cytotoxic cells showed a moderate negative correlation with Treg ($\rho=-0.285$), which was one of the most pronounced values in the matrix. Such a relationship may indicate real functional antagonism: with the strengthening of the regulatory link, cytotoxic activity is suppressed, which was previously described as one of the mechanisms of tumor immunoevasion. The CD4⁺/CD8⁺ ratio demonstrated insignificant correlations with other variables, with the exception of a moderate negative correlation with NK cells ($\rho=-0.191$), which was apparently associated with structural reorganization of the

immune response during surgical stress, when innate cytotoxicity is activated compensatorily in the event of an imbalance in T populations. NK cells generally demonstrated independent behavior with weak correlations with most parameters, with only a slight positive correlation with Treg ($\rho=0.183$).

The key proinflammatory mediator IL-6, which in some cases was considered as a universal marker of surgical stress, did not show a reliable correlation with either TNF- α ($\rho=0.007$), or IFN- γ ($\rho=0.085$), or IL-10 ($\rho=0.087$).

IFN- γ , on the contrary, turned out to be weakly correlated with almost all other parameters. This cytokine has a relative autonomy as a marker of cytotoxic functionality, which is especially important in the context of tumor immune control. Its weak association with IL-10 ($\rho=0.008$) and CRP ($\rho=0.078$) confirms that the antitumor cytokine link functions independently of the classical inflammatory axis. IL-10 is of interest. Its negative correlation with CRP ($\rho=-0.187$) may indicate an inhibitory effect of IL-10 on the synthesis of acute phase proteins, but the strength of the association is insufficient to conclude about a direct regulatory interaction, which also illustrates the general focus on restraining the systemic inflammatory response upon activation of the suppressive link. CRP, as an integral marker of inflammation, was generally found to be weakly associated with cytokine variables, which is probably due to its delayed kinetic profile and dependence on other, in particular, non-functional factors, such as age, BMI, tumor stage and preoperative load.

Of interest is the negative value between NK cells and IL-10 ($\rho=-0.187$), which may potentially reflect biological competition between the active innate response and anti-inflammatory control. A decrease in NK cells with a simultaneous increase in IL-10 may be one of the mechanisms that ensure the weakening of cytotoxic surveillance in favor of inflammatory balance. CD4⁺ T helpers showed weak positive relationships with IFN- γ ($\rho=0.196$) and IL-10 ($\rho=0.134$), reflecting their central role in coordinating both proinflammatory and suppressor responses. However, low values of the coefficients confirm that in the acute postoperative period it is inappropriate to analyze CD4⁺ in isolation from Tregs and cytokines, since a comprehensive interpretation is important. Finally, the CD4⁺/CD8⁺ ratio demonstrated the highest negative value with CRP ($\rho=-0.187$), which may reflect the relationship between systemic inflammation and imbalance in the T-cell link.

Based on the data obtained, we constructed a multivariate logistic model to determine the contribution of each immunological indicator to the risk of an unfavorable clinical outcome. The integral unfavorable outcome, i.e. a low total score on the clinical scale, was considered as a dependent variable.

Among all the analyzed parameters, the highest AUC value was recorded for IL-6 (AUC=0.602), which reflects a moderate but stable discriminatory ability of this cytokine in identifying patients prone to the development of severe immunosuppression and complicated postoperative course.

The Treg indicator demonstrated a weak but potentially clinically significant prognostic ability (AUC=0.523). Despite the modest sensitivity level (37.5%), the specificity was 86.4%, which allows us to consider Treg as a parameter that allows us to confirm the already suspected immune inhibition, especially in combination with other markers. On the contrary, the CD4+, NK and IFN- γ indicators did not demonstrate high individual diagnostic value (AUC <0.5). CD4+ and IFN- γ showed an inverse relationship with risk, but their sensitivity level was extremely low (12.5% and 9.3%, respectively), while the specificity of CD4+ was high (95.5%), which allows us to potentially consider it as a clarifying criterion in a comprehensive assessment. NK cells showed hypersensitivity (100%) with extremely low specificity (13.6%), which makes them applicable only as an early signal of general activation of the immune axis, but not as a discriminatory risk predictor. Based on the data obtained, we have developed a scoring scale "SIDAP" (degrees of immunological acceptability of the anesthetic approach) for cancer patients, implemented as a software module in digital format. The "SIDAP" program provides for patient assessment by five key immunological indicators, each of which is interpreted according to a three-level system: 0 points - no deviations, 1 point - moderate changes, 2 points - severe impairment. Threshold values for each criterion are determined based on ROC analysis and confirmed by expert clinical interpretation. This scale forms an objective basis for personalized selection of anesthetic management method, reducing the risk of worsening postoperative immunosuppression and opening up opportunities for early correction of immune imbalance.

I degree of immunological tolerance (0-4 points), II degree of immunological tolerance (5-7 points), III degree of immunological tolerance (≥ 8 points).

Comparative analysis of the distribution of patients by degrees of immunological tolerance (I-III) in groups I and II at the stage of inclusion in the study demonstrated the comparability of the initial immune profile. The assessment was carried out before immunocorrective measures and before the choice of anesthetic tactics, solely on the basis of laboratory parameters included in the SIDAP scale.

In both groups, patients with a limited or low degree of immunological tolerance predominated, which reflects the high prevalence of immunosuppressive changes in cancer patients before surgery. The proposed method for correcting perioperative immunosuppression and choosing anesthetic tactics in cancer patients is based on a

step-by-step clinical and immunological stratification of the risk of developing immune disorders in response to surgery. It is based on the author's scale of immunological tolerance to anesthesia, taking into account five key indicators of immune status.

At the first stage of the treatment and diagnostic algorithm, a laboratory examination of the patient is carried out, including the determination of five main immunological indicators. The interpretation of the values is carried out according to the SIDAP scale developed by us. Further tactics are determined depending on the degree of SIDAP.

If the first degree of tolerance (SIDAP-1) is present, the patient is considered immunologically resistant. In this case, anesthetic tactics do not require restrictions: general, regional or combined anesthesia can be used depending on the scope of the operation, the anatomical zone and the preferences of the anesthesiologist.

When the second degree of acceptability (SIDAP-2) is detected, the patient shows moderate violations of one or more indicators: decrease in CD4+ to 30-35%, decrease in NK to 10-12.9%, increase in Treg to 6.1-7%, increase in IL-6 to 45 pg/ml and decrease in IFN- γ to 6.5-7.4 pg/ml. In this case, the patient is considered conditionally acceptable for general anesthesia, but priority is given to combined or regional methods. At the same time, moderate immunocorrection is recommended, aimed at stabilizing the inflammatory background and supporting cellular immunity. Moderate and metabolically targeted immunocorrection is recommended, aimed at reducing the level of IL-6, supporting the function of NK cells and moderate inhibition of the proinflammatory cascade. These measures make it possible with a high probability to improve the immune profile indicators and reduce the risks during general or combined anesthesia. The correction program includes four main elements. Celecoxib (COX-2 inhibitor), 200 mg 2 times a day for 3 days before surgery, in order to reduce the level of IL-6 and TNF- α by reducing the production of proinflammatory mediators.

In order to stabilize the cell membrane, neutralize free radicals, protect NK and CD4+ lymphocytes, antioxidant support is prescribed: N-acetylcysteine (NAC): 600 mg \times 2 times a day, orally or parenterally; Vitamin C: 1000 mg / day orally, in 2 doses of 500 mg; Vitamin E: 100 mg / day, orally in capsules. The duration of therapy is 3 days before surgery.

In order to stimulate IFN- γ synthesis, support lymphocyte function and cytotoxic activity, nutritional support (immunonutrition) is prescribed, which includes the use of L-arginine 2-3 g, Glutamine 2 g, Zinc 15-20 mg, Selenium 100-150 mcg, which can be taken in the form of ready-made mixtures (for example, Impact®, Nutridrink® Protein Plus), in a volume of 400-600 ml / day in 2-3 doses per day for 72 hours before surgery. The use of immunonutrition has been proven effective in preparing cancer patients for abdominal surgery. In order to reduce Treg activation, avoid immune inhibition caused

by opioids (to achieve minimization of the opioid load), morphine and its derivatives (fentanyl, tramadol) are replaced with paracetamol (1 g \times 4 times a day); meloxicam (15 mg orally once a day); ketorolac (30 mg intramuscularly); regional analgesia, if possible (blockade, infiltration, epidural analgesia); dexmedetomidine (0.2-0.7 mcg/kg/h intravenously in a perfusor, as indicated, especially in cases of high anxiety and unstable hemodynamics).

Patients with the third degree of immunological tolerance according to the SIDAP scale (total score of 8 points or higher) have severe immune disorders characterized by a persistent decrease in CD4+ and NK cells, an increase in IL-6 and Treg levels, and a decrease in IFN- γ . This profile is associated with a high risk of developing postoperative immunosuppression, delayed recovery, infectious complications, and worsening oncological outcomes. Therefore, general or combined anesthesia without preliminary immunological preparation is contraindicated in this group. In order to stabilize the immune status and transfer the patient to a safer category, a mandatory course of immunocorrection is carried out for at least 72 hours before the planned intervention, including: Celecoxib, NSAIDs and multimodal analgesia, nutritional support (immunonutrition), antioxidants (support of cellular homeostasis), immunomodulators (for the purpose of direct stimulation of the Th1 response and / or suppression of Treg) and the use of transfer factors, Reaferon-Lipint (IFN- α 2b) 500 thousand IU, orally, 1 time per day.

After 72 hours from the start of immunocorrection, a repeated laboratory assessment of the immune profile is carried out, recalculation of points on the SIDAP scale and reassessment of the degree of admissibility. If the patient moves to stage II or I, combined or general anesthesia is acceptable; if stage III remains, the operation is performed under regional support or postponed until the immune status is stabilized.

Thus, the described course of mandatory immunocorrection allows us to transfer patients from the high-risk zone to the controlled one, reducing the likelihood of developing postoperative immunosuppression, complications and violations of antitumor surveillance. It provides the opportunity to choose an anesthetic approach consistent with the state of the immune system and introduces the principle of immunological responsibility into the practice of oncoanesthesiology.

The data obtained confirm the high efficiency of the proposed immunocorrection program. More than 40% of patients who initially had grade III immunological tolerance were able to achieve a risk reduction to grade II or I. As a result, the dynamics allowed us to expand the range of acceptable anesthetic interventions, reduce the need for delays, and ensure the implementation of safer individualized tactics.

The developed treatment and diagnostic algorithm for choosing an anesthetic tactics and correcting perioperative immunosuppression in cancer patients is based on a quantitative assessment of the immunological status using the original scale of immunological tolerance (SIDAP). The scale takes into account five key indicators: CD4+, NK, Treg, IL-6 and IFN- γ , allowing to objectively determine the degree of risk of immunosuppression development during general or combined anesthesia.

In general, immunological correction performed before surgery ensured the formation of a more stable, adaptive immune phenotype in patients, which was expressed in a lesser severity of the postoperative decline in key lymphocyte populations, a more stable functional index and limited growth of the regulatory link. Against the background of general anesthesia, where the most pronounced immune shifts were observed in group I, in patients with immunocorrection they were mitigated by almost 1.5-2 times, which emphasizes the practical significance of the developed preparation algorithm. In comparison with group I, where such measures were not carried out, the dynamics of inflammatory and regulatory markers turned out to be not only more moderate, but also biologically more coordinated, reflecting a weakening of the proinflammatory response and the preservation of adaptive stability. At the stage of preoperative preparation, most patients in Group II showed a moderate decrease in IL-6 and TNF- α levels, which can be interpreted as preventive suppression of subclinical inflammation.

Immunocorrection in the preoperative period is able to modulate the patient's inflammatory reactivity and form a more physiological cytokine response. A decrease in the amplitude of IL-6 and TNF- α , stabilization of IFN- γ and limitation of hyperproduction of IL-10 and CRP create the prerequisites for maintaining the immune balance under surgical stress. The correction effect was especially pronounced when using regional or combined anesthetic approaches, where the cytokine profile indicators demonstrated the best preservation.

The combined approach to the choice of anesthesia (OA + RA) provided a moderate need for additional analgesia in most patients in Group I. After immunocorrection, this number decreased by 17%, and the number of patients who did not need correction of pain relief almost doubled.

Awakening delay in OA with signs of cognitive disorientation was recorded in 2 patients in Group II versus 6 in Group I. At the same time, 7 out of 20 patients in the main group woke up quickly and calmly, while in the control group there were less than a quarter of them.

The subgroup of patients with RA demonstrated the clearest contrast: all 10 patients in Group II woke up without delays and side effects. In Group I, a delay was recorded in

one patient, but the total number of those who woke up perfectly was 20% lower ($p < 0.05$).

The use of combined (OA + RA) anesthesia after immunocorrection showed good results in 10 patients (1.4 times more often than in Group I). Clinically, this was accompanied by a reduction in the duration of post-anesthesia observation.

With OA in Group I, a quarter of patients had severe side effects (vomiting, chills, agitation). In Group II, this indicator decreased almost 5 times, while the proportion of patients without side effects increased by 30% ($p < 0.01$). Side effects in Group I with RA were observed in half of the patients, but required intervention in only 1 case. In Group II, side effects were virtually absent: 12 patients (60%) passed the postoperative period without complaints, which is significantly higher compared to the control subgroup. The proportion of patients with clinically significant side effects in OA + RA decreased from 2 to 1 case, and the number of patients without symptoms increased by 1.6 times, which further confirms the protective effect of immunocorrection and the gentle neurovegetative profile of combined anesthesia.

6 patients in Group I required observation for more than 24 hours after OA. After immunocorrection, there was only 1 such patient, which demonstrates a decrease in the severity of the postoperative period. The number of patients who did not need intensive care increased almost twofold ($p < 0.01$). Even in Group I, patients with RA generally did not require intensive care. But in Group II, there was not a single case of even short-term intensive care control, which emphasizes that the regional component in combination with immune preparation almost completely eliminates the need for resuscitation support. Among patients in group I after OA+RA, 3 cases required observation for >24 hours. In group II - only 1. Good results were assessed in 9 patients versus 8 in group I, i.e. the improvement was pronounced, but moderate.

In Group I, 7 patients did not recover their activity within the first 48 hours after OA. In Group II, there were only 2 such patients. The number of patients who got up within the first day increased by 30%, reflecting both a decrease in inflammation and better autonomic adaptation. In Group II, 11 patients (55%) demonstrated complete recovery within 24 hours after RA, while in Group I there were only 8 such patients. Negative dynamics were not recorded in any patient in Group II. After immunocorrection, the proportion of patients with OA + RA who got up within the first 24 hours increased by 40%, and the number of late mobilizations (more than 48 hours) decreased threefold, which confirms the beneficial effect of the combination of techniques and immune intervention. In general, the introduction of immunocorrection allowed not only to reduce the number of clinically unfavorable scenarios, but also to significantly increase the proportion of patients with the most favorable postoperative status, which confirms

the real clinical value of the approach. The effect is especially pronounced in patients who received regional or combined anesthesia, where stabilization of the immune background was supplemented by the physiological advantage of the method. Thus, the comparative assessment of the effectiveness of the proposed treatment and diagnostic algorithm for the correction of perioperative immunosuppression in cancer patients showed its high clinical effectiveness. The use of immunocorrection before surgery ensured a significant improvement in the indicators of both cellular and humoral immune responses, with a limitation of the severity of the inflammatory cascade, a decrease in the level of proinflammatory cytokines and stabilization of the activity of regulatory links.

Conclusions:

1. The comparative evaluation of the effectiveness of the proposed treatment and diagnostic algorithm for the correction of perioperative immunosuppression in cancer patients showed its high clinical effectiveness. The use of immunocorrection before surgery provided a significant improvement in the indices of both cellular and humoral immune responses, with a limitation of the severity of the inflammatory cascade, a decrease in the level of proinflammatory cytokines and stabilization of the activity of regulatory links.
2. Analysis using the integrated clinical scale for assessing effectiveness demonstrated a significant decrease in the proportion of unsatisfactory outcomes in the main group - more than 2 times, with a simultaneous increase in the proportion of good clinical profiles by 43% ($p < 0.05$). The most pronounced positive effect was recorded with regional and combined anesthesia, which emphasizes the synergism between immunological preparation and the physiological nature of the anesthetic approach.

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