PERIOPERATIVE IMMUNE RESPONSE ALTERATION. CAN IT INFLUENCE CANCER RECURRENCE?

Irina Ristescu¹,², *, Ioana Grigoraș¹,², E. Dumitras¹, G. Dimofte¹,³
“Grigore T. Popa” University of Medicine and Pharmacy Iași
Faculty of Medicine
1. Department of Surgery (I)
Regional Institute of Oncology Iași
2. Anesthesia and Intensive Care Department
3. Surgery Department
*Corresponding author. E-mail: iristescu@yahoo.com

PERIOPERATIVE IMMUNE RESPONSE ALTERATION. CAN IT INFLUENCE CANCER RECURRENCE? (Abstract): The relationship between host immune response and tumor cells is currently defined by the immunoediting concept, including three phases: elimination, equilibrium and escape. Cancer cells are initially eliminated by the immune system, but progressively can develop escape mechanisms. The balance between elimination and escape depends on the prevailing activity of cytotoxic Th1 or immunosuppressive Th2 lymphocytes. Surgery has the potential to eradicate the disease, but, along with other perioperative circumstances, can induce a variable degree and period of immunosuppression. By modifying the Th1/Th2 ratio, these perioperative circumstances may favor the escaping mechanisms and, consequently, promote cancer recurrence and metastasis altering long term prognosis of cancer patients. Keywords: CANCER, SURGERY, ANESTHESIA, PERIOPERATIVE PERIOD, CANCER RECURRENCE, IMMUNOSUPPRESSION.

Cancer represents today a major source of morbidity and mortality worldwide. In the United States, the risk of developing any type of cancer during a lifetime is currently estimated at one in two for men and one in three for women. A report of American Society of Clinical Oncology states that, in 15 years from now, the prevalence of the disease will markedly increase and cancer will exceed heart diseases in terms of mortality, becoming the leading cause of death (1).

Facing this reality, researchers from around the world are struggling to find new early diagnostic strategies and to improve actual therapeutic armamentarium. Despite the introduction of new screening tools, cancer is diagnosed in the clear majority of patients when tumor cells compromise the organ function. However, the leading cause of death in cancer patients is not related to the complications of primary tumor, but rather with the occurrence of local recurrence and distal metastasis (2).

Risk factors for cancer recurrence are multiple, depending on the initial stage of disease, biological features of the tumor, initial therapy and immune function. In clinical practice the modifiable factors are the quality of the applied treatment and the abil-
It is to influence the patient immune system.

The current multimodal approach of cancer patients includes chemotherapy, radiotherapy, surgery and immunotherapy. Surgical resection is the primary treatment in solid tumors and has a curative intent in localized disease. By the same time, the surgical procedure, along with other perioperative interventions, can induce variable degrees and periods of immune suppression, favoring cancer cell spread.

Consequently, we may conclude that the perioperative period in cancer patients is related to the following dilemma: surgery represents the unique possibility to eradicate the tumor, but in the same time has the risk to promote the development of metastasis and alter the long-term outcome of cancer patients.

**IMMUNE RESPONSE IN CANCER PATIENTS**

The immune system plays an important role in the control of tumor growth. The initial theory of immune surveillance, formulated in 1957 by Burnet and postulating that lymphocytes are continuously recognizing and eliminating tumor cells (3), is now replaced by the immunoediting concept. Per this concept immunoediting has three phases: elimination, equilibrium and escape (4,5). In the **elimination phase**, tumoral cells are initially recognized by the innate immune system cells (macrophages) that are activated and migrate to lymph nodes to promote activation and clonal proliferation of cytotoxic T lymphocytes. Those cells migrate to the tumoral site and release enzymes responsible for tumor cell lysis (6). NK cells are also involved in the antitumoral response. The cytotoxic effect of cytokine activated cells is achieved by releasing perforins and granzymes responsible for tumor cell lysis (7). The presence of a T lymphocyte CD8+ and memory T lymphocytes (CD45RO+) infiltrate in the tumoral surrounding tissue is considered a favorable prognostic factor (8). In the **equilibrium phase** of the immunoediting concept, cancer cells, which have survived the elimination process, start to develop genetic mutation and progressively become resistant to the immune system. The **escape phase** is characterized by clinically apparent tumor, due to uncontrolled cancer cells proliferation. There are multiple mechanisms of tumor cells escape from the control of immune system - lack of recognition of tumor cell (lack of tumor antigens expression or MHC gene mutations), peritumoral inflammation that can inhibit the activation of CD8+, CD4+ T lymphocytes, tumor cells may induce the occurrence of Treg cells (9).

CD4+ T helper lymphocytes (Th1 and Th2 subpopulations) modulate the immune system response and can have both stimulatory and suppressive effects on cancer cells. Th1 lymphocytes secrete proinflammatory cytokines (IFN γ, IL-2, IL-12 and TNF-α) and promote an inflammatory response. Th2 lymphocytes synthesize cytokines with anti-inflammatory activity (IL-4, IL-5, IL-8, IL-10 and IL-13). The predominance of Th1 cell activation is associated with an anti-neoplastic immune response. Thus, IL-2, considered the prototype interleukin of Th1 cells, increases the cytotoxic activity of NK cells, induces the synthesis of IFN γ and activate macrophages. In contrast, Th2 cytokines promote the expression of Treg, matrix metalloproteinases, invasiveness and metastasis. In the elimination phase the Th1/Th2 balance favors Th1 cells activity while the escape phase is characterized by a Th2 shift.
RISK FACTORS FOR IMMUNE SUPPRESSION DURING PERIOPERATIVE PERIOD

Cancer patients scheduled for surgery have already, in the preoperative period, multiple sources of immunosuppression. Cancer itself is frequently accompanied by an alteration of both humoral and cellular immune response (10). Neoadjuvant therapies (chemo/radiotherapy) produce destruction of cancer cells, but also of immune cells. Malnutrition and cancer cachexia, caused by systemic and local effects of the tumor depending on the size, location, histological type and stage, but also by treatment side-effects, is associated with a decreased cytotoxic activity of NK cells (11) and reduced levels of cytokines involved in the differentiation of Th1 lymphocytes (12).

Psychological stress and depression is frequently associated with cancer diagnosis and treatment. It triggers a neurohumoral response, characterized by an increased release of catecholamines and glucocorticoids, a reduction of NK cytotoxicity and a proinflammatory status and is correlated with cancer progression (13, 14).

The immunosuppressive effect of surgery is currently explained by the dual action of tissue trauma and surgical stress response. Surgery induces tissue damage and release of cellular debris, that will promote an inflammatory reaction. Proinflammatory cytokines (TNF alfa, IL-1, IL-6) activate hypothalamic-pituitary-adrenal axis and increase cortisol production with suppressive action on the immune system. But surgery also triggers a neurohumoral stress response, consisting of acute inflammation and hypothalamic-pituitary-adrenal axis and sympathetic nervous system activation. This complex response, proportional with the magnitude and invasiveness of surgical injury, aims initially to adapt the organ function to increased demands. When prolonged or exaggerated, this adaptive response can become harmful. The cumulative effects of released cortisol and catecholamines on immune function promote a Th2 cell dominance, with a consecutive depression of cellular immunity lasting for several days after surgery (15, 16). Oncologic surgery often requires extensive tissue excision/resection, being associated with a high risk of intraoperative bleeding, hypovolemia and hypotension. The consecutive activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis along with reduced tissue perfusion and tissue hypoxia will depressed the Th1 lymphocyte response (17). The perioperative hyperglycemia is the result of increased hepatic glycogenolysis and gluconeogenesis and peripheral insulin resistance. It impairs normal phagocytosis and leukocytes function and releases pro-inflammatory cytokines (18).

Perioperative anemia is a frequent finding in oncologic surgical patients due to preoperative bleeding, malnutrition, side-effects of neoadjuvant therapies and intraoperative blood loses. Immune suppressive effect of allogeneic blood transfusion is currently termed transfusion-associated immunomodulation (TRIM) and is characterized by the reduction of Th1 lymphocytes and NK cells count (19, 20).

Multiple techniques and drugs are available to provide appropriate anesthesia during surgery. Their influence on the long-term outcome seems to be explained by the modulation of the neuroendocrine response to stress and by the interaction with the immune system. Anesthesia and analgesia effects on immune function depend on the type of technique used (general anesthesia,
locoregional anesthesia or combined general anesthesia/locoregional analgesia) and the type of hypnotic and analgesic drugs. Concerning the choice of the anesthesia technique, two major retrospective analyses showed that using intraoperative locoregional analgesia instead of postoperative intravenous morphine analgesia markedly reduce cancer recurrence (21-22). This potential benefit of regional anesthesia/analgesia techniques can be explained by the attenuation of surgical stress response and the reduced intraoperative doses of opioids and inhalation drugs (23). Intravenous anesthetic drugs like ketamine, thio-pental and midazolam result in a significant reduction of NK cells activity, as shown in animal studies (24-25). Conversely, propofol administration has no influence on NK cells and seems to favorably increase Th1/Th2 ratio in the postoperative period (24,26). Currently used volatile anesthetic agents like isoflurane and sevoflurane suppress NK cells activity and impair various lymphocyte functions in a dose and time dependent manner (23,27). Opioids induced immunosuppression was extensively studied in cancer patients. Morphine administration was associated with Th2 differentiation and increased glucocorticoid production (28-30). Conversely, the use of fentanyl and tramadol seems to increase the number and activity of NK cells, having protective antitumoral effects (31-32).

CONCLUSIONS
The complex interplay between immune system response and tumoral cells growth can influence cancer progression. Surgical interventions in oncological patients are focused on tumor eradication. The surgical stress response triggers a complex neuro-humoral and immune reaction. Acting on an already altered immune status, the surgical procedure, anesthesia and other peri-operative circumstances, induce a variable degree and period of immunosuppression, creating a window of opportunity for cancer recurrence and distal metastasis.

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