DOI: 10.15825/1995-1191-2021-3-192-197

POST-TRANSPLANT MALIGNANCIES IN SOLID ORGAN RECIPIENTS: DEVELOPMENT MECHANISMS AND RISK FACTORS

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According to the International Agency for Research on Cancer, there were an estimated 19,292,789 new cancer cases in various localizations and 9,958,133 cancer deaths worldwide in 2020. These frightening figures clearly show that malignancies among the population is a pressing matter. The risk of post-transplant malignancy in solid organ recipients is 2–6-times higher than in the general population. Given the steadily increasing number of solid organ transplants worldwide and the gradual increase in life expectancy among organ recipients, studying the issues concerning risk factors and development mechanisms becomes a crucial task.

Keywords: malignant tumor, transplantation, solid organs.

INTRODUCTION

According to the International Agency for Research on Cancer, the year 2020 had about 19,292,789 new cancer cases and 9,958,133 cancer deaths worldwide. Breast cancer is the most commonly diagnosed cancer in the world, accounting for 2,261,419 cases (11.7%), followed by lung cancer 2,206,771 cases (11.4%), colorectal cancer 1,931,590 (10%), prostate cancer 1,414,259 (7.3%) and stomach cancer 1,089,103 (5.6%). Lung cancer tops the mortality chart with 1,796,144 (18%), colorectal cancer 935,173 (9.4%), liver cancer 830,180 (8.3%), and stomach cancer 768,793 (7.7%). There are some gender differences in cancer incidence in men and women. Among men, lung cancer is the most common (14.7%), followed by prostate cancer (14.1%) and colorectal cancer (10.6 per cent). In women, breast cancer (24.5%), followed by colorectal cancer (9.4%) and lung cancer (8.4%). These frightening figures clearly show the urgency of the problem of malignant tumors among the population [31].

According to reports, the risk of malignant tumors in solid-organ transplant recipients is 2–6 times higher than in the population. Given the steadily increasing number of solid organ transplants worldwide (113,363 solid organ transplants were performed in the world in 2020 alone) and the gradual increase in life expectancy of donor organ recipients, the relevance of studying malignancies would only increase. Issues of cancer development in this category are covered in sufficient detail in foreign literature, but we did not find any domestic sources [1–13, 30].

EPIDEMIOLOGY

Since the first donor organ transplants, there has been increased risk of cancer cases among solid-organ transplant recipients [1, 2, 6–10]. Most authors conclude that within the next decade, malignant tumors will become the leading cause of death in this patient category [3, 4, 11–13]. As life expectancy increases, so does the importance of the problem of cancer [2, 14].

The literature contains numerous data on the occurrence of malignant tumors in solid-organ transplant recipients. The authors, analyzing the groups of recipients diagnosed with cancer, differing by age, sex, transplanted organ, country of residence, etc., confirm the relevance of this problem. For example, Wareham N.E. et al., who studied the data of 212 solid-organ transplant recipients with malignant tumors found that cancers were the second among liver recipients, third among kidney recipients, and fourth most common cause of death among lung recipients in 5 years after transplantation. The authors concluded that the causes of cancer are primarily related to immunosuppressive therapy, as well as the presence of precancerous diseases [6, 7].

Based on analysis of 8,520 cancer cases among 164,156 solid-organ transplant recipients, Hall E.C. et al. found that with the exception of nonmelanoma skin cancer, non-Hodgkin's lymphoma (NHL) (one of the adverse outcomes of post-transplant lymphoproliferative disorder (PTLD)) is the most common malignant tumors in solid-organ transplant recipients [1, 11, 12].

According to E. Yanik et al., among 187,384 solid-organ transplant recipients, including kidney (58%), liver (22%), heart (10%) and lung (4%), 9,323 cancers (4.97%) were identified. The most common malignant tumors were lung cancer (N = 1993), NHL (N = 1846) and prostate cancer (N = 1544) [15].

The risk of cancer in solid-organ transplant recipients, according to Guillemin A. et al., is 2.6 times higher than

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in the general population and is the third most common cause of death among this category of patients [5].

Vajdic C. et al. reports that solid organ recipients have a 3-fold higher risk of developing cancers compared to the general population [16].

In a study by S. Acuna et al. who evaluated 11,061 solid-organ transplant recipients, malignant tumors were the second cause of death after cardiovascular diseases. Of the recorded deaths in this study cohort, 20% were attributed to the development of cancer, the majority (68%) of which occurred in de novo cases, 11% (1,267 patients) developed a de novo malignancy within 5 years of transplantation. Mortality from nonmelanoma skin cancer (squamous cell and basal cell cancer) in solid-organ transplant recipients is 30-fold higher than in the general population, and the mortality rate from NHL is 10 times higher than in the population [17].

According to reports from E. Neval et al., among the 1656 solid-organ transplant recipients studied, the most frequent type of cancer was skin cancer (121 patients), then lymphoma (non-Hodgkin and Hodgkin), 37 patients) and lung cancer (19 patients) [2, 16].

Z. Huo et al. found that the risk of lung, liver, and kidney cancers was mainly increased in heart and/or lung recipients, liver recipients, and kidney recipients, respectively [18].

In a cohort study that analyzed the frequency of malignancy in 175,000 solid organ transplant recipients, Brennan D.C. et al. noted a more than 5-fold increase in incidence of Kaposi sarcoma, nonmelanoma skin cancer, non-Hodgkin lymphoma, liver cancer and anogenital cancer. And there was also a significant increase in other cancers: lung, kidney (in lung and kidney recipients, respectively), colorectal, pancreatic, Hodgkin's lymphoma, and melanoma. In contrast, the incidence of breast cancer and prostate cancer was lower [19].

According to A.-M. Noone et al., among the 221,962 solid organ recipients studied, 15,012 developed cancer (6.76%). Lung cancer was the largest contributor to mortality (3.1%), followed by non-Hodgkin lymphoma (1.9%), colorectal cancer (0.7%), and kidney cancer (0.5%). NHL was the largest contributor among children (4.1%), and lung cancer among 50+ year-olds (3.7–4.3%). Mortality attributable to cancer increased steadily with longer time since transplant, reaching 15.7% of deaths 10+ years post-transplant [20].

Thus, despite some inconsistency in the data obtained by different authors, the risk of malignant tumors such as lymphomas (Hodgkin and non-Hodgkin lymphomas), lung cancer, skin cancer and colorectal cancer is higher in solid organ transplant recipients than in the population.

PATHOGENESIS

There are three main mechanisms of cancer development in solid organ transplant recipients: development of de novo malignancy; transplantation of an organ containing malignant tumor (primary or metastasis); progression of a neoplastic process existing in the recipient before transplantation [8, 18]. According to many authors, there are a number of factors associated with development of malignant tumors in solid-organ transplant recipients, including: the nature and duration of immunosuppressive therapy, concomitant viral infection, sun exposure (for skin cancer), a history of pre-transplant dialysis in kidney recipients (the risk of renal cell carcinoma is associated with formation of acquired polycystic kidney disease, occurring in patients on hemodialysis for a long time), and episodes of acute rejection [1, 7, 11, 16–22]. Additional risk factors common to the general population also include smoking, alcohol abuse, and age of the recipient [23]. It is important to note that we have an incomplete understanding of how immunosuppressive drugs actually contribute to the development of malignancies. The high risk of PTLD associated with the use of anti-T-cell antibody induction is almost certainly associated with intense immunosuppression and a consequent decline in immunosupervisory functions [24, 25]. Immunosuppressants lead to immune suppression in recipients, thereby reducing antitumor and antiviral defense, and they can also have a direct damaging effect on the recipient's DNA (e.g. azathioprine increases the risk of malignant tumors and especially squamous cell skin cancer due to its mutagenic effect and potentiation of the adverse effect of ultraviolet light) [7, 17, 26]. Immunosuppressive therapy directed against T-lymphocytes (antithymocyte globulin) predisposes to the development of Epstein–Barr virus-induced PTLD [7, 15]. On the contrary, therapy with antibodies targeting B-lymphocytes (rituximab) does not increase the incidence of malignancies [8].

There is a correlation between the likelihood of developing malignant tumors and increased levels of immunosuppression. For example, heart transplants often maintain high levels of immunosuppression, unlike kidney transplants, because of the risk of death associated with organ rejection. In a study of more than 50,000 kidney and heart transplants, the incidence of PTLD was highest in the first year when immunosuppression was the highest, it declined by 80% thereafter. Incidence of malignant neoplasms was significantly higher in heart recipients, which was consistent with a greater degree of immunosuppression in these patients [18]. Episodes of transplant rejection in the first year after transplantation increase the likelihood of malignancy, apparently due to high doses of immunosuppressive drugs used in the event of a rejection crisis [16, 17, 22]. The different incidence of cancers in different solid organ recipients may be related to the direct effect of immunosuppressive drugs [1, 8, 12, 16, 18, 19]. There is a dose-dependent association between calcineurin inhibitors and malignant tumors, such as lymphoproliferative disorders or skin cancer. In contrast, sirolimus and other M-TOR inhibitors have a direct antitumor effect [19]. Some authors have reported

reduced risk of malignancies against the background of taking sirolimus (in comparison with controls, sirolimus use reduced the risk of malignant neoplasms by 40% and reduced the risk of nonmelanoma skin cancer by 56%) [7, 11, 14, 18, 19], others note no such effect [19]. In vivo experimental studies have shown that azathioprine increases the risk of malignant neoplasms and, especially, squamous cell skin cancer due to its mutagenic effect and potentiation of the adverse effect of ultraviolet light [3, 5, 7, 8]. Cyclosporine increases the risk of Kaposi's sarcoma and metastatic lung injury in patients with glandular cancer [3, 5, 7, 8]. Brennan D.C. et al. cites data from a study of 231 renal allograft recipients. Patients receiving low-dose cyclosporine (75 to 125 ng/mL) for 12 months had a lower incidence of all malignancies (23 versus 37 diseases), especially skin cancer (17 versus 26 diseases) compared to the group of patients receiving conventional doses of cyclosporine (150 to 250 ng/mL). The median follow-up was 66 months [19]. According to Brennan D.C. et al., the use of tacrolimus increases the risk of malignant tumors after kidney transplantation. The carcinogenic effect of calcineurin inhibitors is achieved mainly due to stimulation of transforming growth factor beta (TGF-β) secretion by cells and increased expression of vascular endothelial growth factor [8]. Solid organ recipients receiving mycophenolate mofetil have a lower risk of cancer, which may be associated with reduced incidence of acute rejection, which in turn leads to lower need for increased doses of immunosuppressive drugs [5, 7]. The role of corticosteroids in development of malignancies is difficult to assess because they are almost always prescribed simultaneously with other immunosuppressants [5].

According to the majority of authors, the presence of oncogenic viruses, or their transmission with the donor organ is a significant risk factor for cancer development against the background of prolonged immunosuppression. For example, Epstein–Barr virus is the main provoking factor of non-Hodgkin's lymphoma and Hodgkin's lymphoma, which are malignant forms of PTLD. Anogenital cancer is associated with human papillomavirus and Kaposi's sarcoma with herpesvirus type 8. In these situations, immunosuppression reduces immune control of these viral infections [1, 7, 16, 18, 19, 21, 22]. According to Z. Huo et al., the presence of hepatitis C or B virus is considered a risk factor for liver cancer, and the presence of human papilloma virus can provoke cervical, vulvar, vaginal, penile, anus and oropharyngeal squamous cell cancer. Among solid organ recipients, 90% of patients with squamous cell cancer had human papillomavirus, whereas in the population, the prevalence of human papillomavirus among patients with squamous cell skin cancer ranges from 11% to 32% [18]. According to J. Liao et al., the development of cervical, vulvar and vaginal cancers in solid-organ transplant recipients is also associated with persistent human papillomavirus [28].

If a liver transplant has been performed for primary sclerosing cholangitis or a lung transplant for cystic fibrosis, recipients have an increased risk of colorectal cancer, as up to 80% of recipients with primary sclerosing cholangitis have inflammatory bowel disease (most often non-specific ulcerative colitis, which is a risk factor for colorectal cancer), and in cystic fibrosis there are changes in the gastrointestinal epithelium due to mucus secretion disorders [24]. With unilateral lung transplantation or kidney transplantation, there is increased risk of malignant tumors in the preserved native organ according to the nosological form of the original disease that led to transplantation [24]. According to Wareham N.E. et al., elderly age and chronic inflammation were the risk factors for cancer, especially lung cancer [12, 21]. Besides, bad habits leading to end-stage disease in solid-organ transplant recipients (for example, smoking in lung recipients and heart-lung complex) also increases cancer incidence [3, 8].

Several authors believe that immunosuppressive therapy may contribute to cancer development from undetected neoplasms prior to transplantation [1, 3, 5, 7, 9]. For example, increased risk of melanoma in solid-organ transplant recipients within 5 years after transplantation may be associated with the presence of a neoplastic process in the donor, undetected before transplantation. In turn, immunosuppression leads to rapid growth and progression of the tumor [24]. Malignant tumors in donor organs (liver, lungs and kidneys), if these organs were obtained from donors with a history of cancer, are diagnosed after transplantation in almost half of cases [1, 5, 9]. Acuna S.A. et al. report that among 22 of those that received heart and/or lung from such donors, malignant tumors developed in 45% of the recipients [19].

Acuna S.A. et al. found that a significant number of patients in need of solid organ transplantation had a history of cancer, representing a group at increased risk of developing a malignant tumor of new localization, as well as pre-existing malignant tumors [29]. According to the literature review and meta-analysis by S. Acuna et al., the overall rate of cancer recurrence after solid organ transplantation in patients with a history of cancer prior to transplantation is 6%. The lowest risk of cancer recurrence was in liver transplant recipients, and the highest was in kidney transplant recipients [29].

Despite the fact that report from the IPITTR (Israel Penn International Transplant Tumor Registry) study showed that the rate of cancer recurrence after kidney transplantation in patients with a history of cancer before transplantation was 21% (the majority (53%) had surgery in the first 2 years after diagnosis or treatment of cancer). S. Acuna et al. argues that we should be skeptical about these data. As in IPITTR, patients are registered voluntarily, without the obligation of further long-term monitoring [29]. Current English-language guidelines for selection of kidney transplant candidates recommend

different waiting times before transplantation for patients with a history of cancer before transplantation. The waiting period can range from none at all for some malignancies in situ, to more than 5 years for melanoma, bladder cancer, colorectal cancer, and breast cancer. For recipients of other solid organs, transplantation is recommended after complete cure of the tumor, provided that the expected cancer survival exceeds the expected survival after transplantation [29].

CONCLUSION

Malignancies are one of the leading causes of death worldwide, regardless of gender. Despite often contradictory data from different authors, most agree that there is an increased risk of certain types of malignancies in solid organ transplant recipients who routinely take immunosuppressive medications (e.g., skin cancer, colorectal cancer, lung cancer, lymphoproliferative diseases). Besides the well-known risk factors typical for the general population (smoking, viral infections, alcohol abuse, age, gender, etc.), there are specific factors in solid organ transplant recipients, such as the effect of immunosuppressive therapy, not only immune suppression but also the direct effect of immunosuppressive drugs. It is also necessary to mention specific mechanisms of development of malignant tumors in solid organ transplant recipients, such as donor-transmitted tumors.

Analysis of reports shows that as the life expectancy of solid-organ transplant recipients increases, and given the constantly growing number of solid organ transplants, the relevance of early diagnosis of malignant tumors will only increase. Without good knowledge of risk factors and mechanisms of tumor progression in solid-organ transplant recipients, it would be impossible to timely diagnose and prevent cancer in this patient category.

The authors declare no conflict of interest.

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The article was submitted to the journal on 9.08.2021