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CLINICAL FEATURES OF MALIGNANT TUMORS AGAINST THE BACKGROUND OF IMMUNOSUPPRESSIVE THERAPY IN HEART TRANSPLANT RECIPIENTS

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As the survival rate of cardiac recipients improves, higher incidence of malignancy in the late postoperative period becomes essential for their prognosis. Immunosuppressive therapy is one of the key prerequisites for successful transplantation. However, long-term use of immunosuppressive agents increases the incidence of malignant tumors compared to the general population. The risk of their development after organ transplantation increases by 2–4 times compared to the general population. For patients who have undergone transplantation since 2000, the risk of developing malignant neoplasms 1–5 years after surgery is estimated at 10–12%. Timely comprehensive examination of patients, development of new immunosuppression schemes, treatment of those predisposing to the development of malignant neoplasms and giving up harmful habits will reduce the risk of malignant tumors and help diagnose these serious complications at an early stage, which, in turn, will increase the life expectancy of solid organ (particularly the heart) recipients.

Keywords: heart transplantation, immunosuppressive therapy, malignant tumors.

INTRODUCTION

Heart transplantation (HTx) remains the most effective surgical treatment for refractory congestive heart failure. Provided that patient selection criteria are met, HTx can significantly increase patients' life expectancy, improve exercise tolerance and quality of life, and often allow patients to return to work. Apart from organ shortage, the main problems of transplantology are related to lack of effectiveness and safety of immunosuppressive therapy in the long term, which is associated with cellular and/or antibody-mediated graft rejection, infectious diseases, hypertension, renal failure, malignancies, and coronary artery vasculopathy in some patients [1].

In Russia, as elsewhere in the world, the most significant side effects of immunosuppressive therapy are malignancies, infectious complications, nephropathy, and diabetes mellitus [2].

According to the International Society for Heart and Lung Transplantation (ISHLT) report on HTx in adults, based on data submitted by 394 transplant centers observing 104,000 patients worldwide, the median survival after HTx was 8.5 years in recipients operated on between 1982 and 1992 and 10.9 years in recipients operated on from 1993 to 2003. The report concludes, however, that the improvement was mainly due to a decrease in mortality in the first year after HTx and that mortality at a later date did not fall significantly [3]. In 2018, there were reports showing that 16% of patients who lived 5 years after HTx and 28% of patients who lived 10 years after HTx were diagnosed with at least one case of malignancy in one location or the other. Moreover, malignancies are now the leading cause of death in patients who had HTx more than five years ago [4], confirming the importance of research on this topic. As short- and mid-term outcomes improve, long-term HTx complications, such as coronary artery vasculopathy and malignant tumors, become increasingly important. The risk of developing malignancies after organ transplantation is 2–4 times higher than in the general population, with the risk being higher in heart and/or lung recipients than in liver and/or kidney recipients [5–7]. For patients who have already had a transplant surgery, the risk of malignancy 1–5 years after HTx is estimated at 10–12% [8]. Despite the urgency of the problem, there have been relatively few studies on cancer incidence after heart transplantation. The incidence of malignant tumors after heart transplantation has varied widely in previous studies, ranging from 3% to 30%. This wide variation in results is mainly due to the different follow-up periods in different studies and the lack of detection of skin cancer, the most common post-transplant malignancy, in many large studies [9].

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FEATURES OF THE COURSE OF CANCER IN PATIENTS WITH HEART TRANSPLANTS

According to the registry of the University Hospitals Leuven (Belgium), which included 563 patients who underwent primary heart transplantation over 25 years (1987–2013), malignant tumors of various localizations occurred in 181 patients (263 diagnosed cases of various tumors), which was 4511 cases per 100,000 patient-years. The mean age of the patients was 63 ± 11 years, the time after HTx was 7.7 ± 5 years. Screening for post-transplant malignancies was an integral part of follow-up and included clinical examination at each visit, annual chest x-ray, dermatologic examination, and gynecologic examination or prostate-specific antigen testing. Mammography and colonoscopy were performed according to current international guidelines [8]. The cumulative incidence of cancer 1, 5, 10, and 20 years after transplantation was 2% (95% confidence interval [CI], 0–4%), 14% (95% CI, 10–18%), 29% (95% CI, 25–33%), and 60% (95% CI, 52–68%), respectively. The most common cancer type was squamous cell skin cancer (58 patients, 22% of all cancers) and followed by basal cell skin cancer (51 patients, 19%). Many skin cancer patients had primary multiple tumors: 180 cases of squamous cell carcinoma in 58 patients and 111 cases of basal cell carcinoma in 51 patients. Forty-one patients (16%) had lung cancer, 30 (11%) had lymphoma, and 25 (10%) had prostate cancer. Increased risk factors for post-transplant malignancy in univariate Cox proportional hazards analysis were: having HTx before 2000 (hazard ratio [HR] 1.4; $P < 0.047$), older than 50 years at the time of HTx (HR 3.3; $P < 0.001$), male gender (HR 2.1; $P < 0.001$), history of smoking (HR 1.5; $P < 0.010$), immunosuppressive therapy with azathioprine (compared with mycophenolate mofetil, HR 1.4; $P < 0.044$) or with cyclosporine (compared with tacrolimus, HR 1.7; $P < 0.05$), coronary etiology of cardiomyopathy causing HTx (HR 1.4; $P < 0.024$).

Recipient's age at the time of transplantation was the most important risk factor, which is consistent with the data obtained from many registries. The risk of malignancy correlates both with age of patients after transplantation [10] and age of the general population [11]. A possible explanation is the aging of the immune system, which undermines the ability to defend against tumor cells. The aging of the immune system begins in early childhood with involution of the thymus, leading to decreased production of native T cells, and continues throughout life with gradual functional impairment of T cells. In older patients who have undergone HTx, the aging of the immune system is exacerbated by immunosuppressive therapy, which leads to increased risk of malignancy [12].

Another important risk factor was the male gender of the recipient. This was due in part to the higher incidence of prostate tumors in men compared to breast tumors and cervical cancer in women. However, the pattern was also observed after excluding these three diseases, which is consistent with other studies [13–15]. Curiously, the same differences in susceptibility to tumors are also observed in the general population [16]. This phenomenon may be caused by hormonal [17] and sex chromosome-specific effects on immune regulation [18], although the exact mechanisms of this phenomenon remain to be elucidated. Although the introduction of safer immunosuppressive therapy regimens and a reduced risk of cancer in patients operated on after 2000 is encouraging, the risk of malignancy in this localization remains high.

Not only are post-HTx malignant tumors more common than in the population, but they also usually have a poorer prognosis. The average survival for cancers of various localizations in HTx recipients is 2.9 years after diagnosis, which is significantly lower than the survival of patients with similar diseases in the general population [12, 19]. The incidence of tumors in this group of patients and the high mortality rate from them requires constant attention during the entire period of patient follow-up. Since immunosuppressive therapy is probably the most important modifiable risk factor for post-HTx cancer, individualizing immunosuppression may help reduce the risk of complications and, consequently, increase survival and life expectancy in this patient population [8].

A study at HUS Helsinki University Hospital (Finland) analyzed data from 479 adult heart transplant recipients transplanted in 1985–2014 (total of 4491.6 person-years of follow-up) and a mean follow-up of 7.8 years. Of all patients, 415 (86.6%) were alive 30 days and 386 (80.6%) one year after HTx. At the end of follow-up, 234 (48.9%) patients were alive. The mean age at the time of surgery was 52 years, 79.5% of the patients were male. A total of 267 cancers were reported in 143 patients during follow-up; the cumulative incidence after 1, 5, 10, and 20 years was 0.3%, 8.7%, 22.3%, and 52.4%, respectively. 96.3% of all malignant tumors were detected in men. The mean time from HTx to the development of cancer was 8.9 years. Among all patients, 21 had a history of malignancy of various localizations before HTx, of whom 11 (52.0%) were diagnosed de novo in the postoperative period. There were no recurrences of a previous malignancy [20].

Malignant tumors were classified as the cause of death in 52 patients, representing 21.2% of all deaths in the cohort during follow-up. There were only 2 deaths from malignancy within the first year after HTx, and 9 deaths within the first five years after HTx. The cancer risk ratio for the entire cohort of patients after HTx was 3.1 (95% CI 2.4–4.1), increasing slowly over time after HTx: 2.3 (95% CI 0.8–4.9) in the first five years after HTx, 3.0 (95% CI 1.6–4.1) 5.0) at 5–10 years, 3.3 (95% CI 2.2–4.8) at 10–20 years, and 4.6 (95% CI 2.0–8.8) at 20 years after HTx. HR to develop malignant tumour was

higher for men (3.3; 95% CI 2.5–4.3) than for women (1.8; 95% CI 0.5–4.7) and was highest in younger patients: 8.0 (95% CI 2.5–18.6) <40 years old with HTx, 5.8 (95% CI 3.3–9.3) in patients 40–49 years old, 2.0 (95% CI 1.3–3.2) in patients 50–59 years old, and 3.2 (95% CI 1.8–5.2) in patients over 60 years old at the time of malignant tumor detection. The study showed that the incidence of malignant tumors of different localizations in Finnish heart transplant recipients was six times higher and mortality three times higher than in the Finnish population as a whole, which is consistent with data from other studies [21, 22]. Basal cell carcinoma was the most common malignancy in the described cohort – more than half of all detected malignant tumors. Other cancers that were generally common in the Finnish population were also frequent: prostate cancer, lung cancer, and kidney cancer. Nevertheless, the incidence rate for all of them was significantly higher than that of the population, with the exception of prostate cancer. There were many cases of non-Hodgkin lymphoma (n = 36, HR 25.7) and lip and tongue cancer (HR 47.4 and 26.3, respectively).

Results of the study indicate that there is a high incidence of malignant tumors of various localizations among heart and/or lung recipients, the most common of which was squamous cell skin cancer [5, 23, 24]. Because oral cancers are associated with human papillomavirus (HPV) infection [25], chronic carriage of the virus on the background of immunosuppressive therapy has been recognized as a predisposing cause for the development of these cancers in heart recipients [26]. It has been suggested that HPV infection is a predisposing factor in the development of squamous cell skin cancer in heart transplant recipients [27].

The use of polyclonal antibodies to human lymphocytes for immunosuppression is thought to increase the risk of lymphoma and skin cancer. In recent years, along with a decrease in the use of polyclonal antibodies, a decrease in the incidence of lymphoma after heart and lung transplantation has been reported [28]. Squamous cell skin cancer was the most common and more aggressive type of cancer, which emphasizes the importance of regular skin examinations, especially because the disease tended to be more severe in solid organ recipients than in other patients [26]. Further studies are needed to determine the effect of immunosuppressive therapy regimens on the incidence of malignant tumors of various localizations, as well as to identify other possible risk factors for their occurrence in heart recipients.

The increased risk of malignancy in heart transplant recipients requires regular examinations and self-examination. Current guidelines in the Russian Federation include blood testing for Epstein–Barr virus (by polymerase chain reaction), measurement of prostate-specific antigen levels, mammography, and chest X-rays [2].

IMMUNOSUPPRESSIVE THERAPY AS A RISK FACTOR FOR MALIGNANCY AFTER HEART TRANSPLANTATION

Immunosuppressive therapy is one of the key conditions for a successful transplant surgery. However, many studies have reported that long-term use of immunosuppressants after transplantation increases the incidence of malignancy compared to the general population [12, 29].

Immunosuppressive therapy after HTx can be divided into induction and maintenance therapy. Induction immunosuppressive therapy is prescribed for a set period of time after surgery, while maintenance therapy is prescribed for life. Induction immunosuppressants that are used for HTx include rabbit antithymocyte globulin (ATG), equine ATG, and interleukin 2 receptor antagonists (basiliximab). According to the ISHLT registry, induction immunosuppressants were used in 52% of all patients with HTx in 2002 and 47% of all patients with HTx in 2012. In recent years, the preferred type of induction therapy has been ATGs or IL-2 receptor antagonists, which were administered in 27% and 21% of cases in 2002 and in 19% and 28% in 2012 [30]. The fact that only about half of all HTx recipients worldwide receive some form of induction therapy reflects the disagreement over its scope. The benefits include earlier reduction in glucocorticoid (GCS) doses and delayed initiation of calcineurin inhibitors (CIs) without a higher risk of rejection, as shown in randomized [30], retrospective [31] and prospective studies [32]. This avoids the side effects of GCS and the nephrotoxic effects of CIs. However, there are not yet enough large, randomized studies yet to draw conclusions about the safety and efficacy of immunosuppressive drugs used for induction therapy. Their long-term side effects are not yet fully understood, and there are concerns that they may increase the risk of infections and tumors [33]. To remove uncertainty about the potential benefits and harms of induction therapy for HTx, a Cochrane review was conducted in 2013 with a meta-analysis of 22 randomized trials [34]. Mortality and major complications, such as acute and chronic heart graft rejection reactions, development of infections, malignancies of various localizations, and decreased renal function, were studied. When comparing treatment regimens, acute graft rejection reactions were less common with induction therapy. Unfortunately, most of the studies included in the review did not last long enough to assess the risks of malignancy after HTx. Therefore, longer studies on this topic are needed to draw a definitive conclusion [35].

Maintenance immunosuppression after HTx usually consists of GCS, CIs (cyclosporine or tacrolimus) and mycophenolate mofetil, azathioprine or m-TOR inhibitor (everolimus or sirolimus). CIs inhibit the calcineurin enzyme in T cells, thereby preventing their proliferation and differentiation, while the antimetabolites

azathioprine and mycophenolate mofetil in turn inhibit the cell cycle of T and B cells, thereby having a more pronounced effect on both T and B cells [36]. According to the ISHLT registry, the frequency of CIs and antimetabolites in patients who survived 1 year after HTx has remained about the same since 2000 (98% and 88% respectively in 2000, 94% and 89% currently). At the same time, by 2012, cyclosporine was prescribed significantly less frequently than tacrolimus (13% versus 81% in patients who lived 1 year after HTx). The advantages of tacrolimus over cyclosporine were shown in a meta-analysis of 10 randomized trials involving 952 patients after HTx [35]. Tacrolimus was less likely to cause arterial hypertension, hyperlipidemia, hirsutism, and gingival hyperplasia, and in some studies, it was associated with lower overall post-HTx mortality. However, there were no significant differences between tacrolimus and cyclosporine in terms of appearance of malignancies and some other complications. Likewise, azathioprine is actively replaced by mycophenolate mofetil (3% versus 85% in patients surviving 1 year after HTx). Everolimus and sirolimus inhibit m-TOR (mammalian target of rapamycin), thereby reducing the proliferation and differentiation of T and B cells [36]. According to the ISHLT registry, the proportion of heart transplant recipients receiving an m-TOR inhibitor 1 year after transplantation increased from 3% in 2000 to 13% in 2012. M-TOR inhibitors are currently being studied for use in patients with chronic kidney disease and graft vasculopathy, but their use is limited by side effects, especially poor wound healing [37]. Everolimus is used not only after HTx but also in the treatment of some malignancies, such as renal cell carcinoma, pancreatic neuroendocrine tumors, and HER2-positive breast cancer [38–40]. The use of sirolimus in kidney recipients reduced the risk of malignant tumors [41, 42]. However, the risk of developing malignant tumors in patients treated with everolimus after HTx is poorly understood, although in a 2016 experimental study, retrospective follow-up of HTx patients showed promising results. At follow-up from March 1, 1990 to March 1, 2015 (mean period, 69.2 months) at the National Taiwan University Hospital in 454 patients receiving combined immunosuppressive therapy, including mycophenolate mofetil (n = 232) or everolimus (n = 222), malignancies were diagnosed in 27, of whom 23 (85%) received mycophenolate mofetil and 4 (15%) received everolimus. Everolimus therapy was significantly safer (9.91% vs. 1.80%, $P < 0.001$). The most common malignancies were lymphoma (n = 7), skin cancer (n = 5), and prostate cancer (n = 3). The 2-year overall survival after detection of malignant tumor did not differ significantly – 50% in the everolimus group and 47% in the mycophenolate mofetil group ($P = 0.745$). Perhaps the benefits of everolimus can be explained by the increased expression of E-cadherin, which promotes inhibition of cyclin-dependent kinase (CDK) $p27^{kip1}$, decreased cyclin D1 expression and cell cycle arrest of the tumor cell in the G1 phase, thus preventing tumor growth and metastatic progression [43].

MALIGNANT TUMORS OF VARIOUS LOCALIZATIONS IN HEART RECIPIENTS

Skin cancer is the most common malignancy seen in transplant recipients, accounting for 42% to 50% of all post-HTx tumors. The average interval between HTx and skin tumor diagnosis correlates with the age of the recipient at the time of transplantation. In general, patients over 50 years of age have a higher risk of developing the cancer than younger patients.

There are both external and internal risk factors for skin cancer. Ultraviolet radiation appears to be the main one [44], since skin cancer develops on areas exposed to prolonged and intense sun exposure, and is more frequently seen in patients exposed to high sun exposure after transplantation (>10,000 hours) [45, 46]. The incidence of skin cancer is directly correlated with the concentration of immunosuppressive drugs and the presence and frequency of rejection episodes in the first year after HTxx [47], more common in people with fair skin (Fitzpatrick type II), blue eyes, and blond or red hair [47, 48, 52]. The likelihood of developing skin cancer after HTx depends on gender [47].

The histologic pattern most often corresponds to squamous cell or basal cell carcinoma [49], localized to the head and neck (70%), trunk (9%), upper extremities (17%), or lower extremities (4%) [50]. Squamous cell carcinoma is 65–250 times more common in patients after HTx than in the general population, basal cell carcinoma is 10 times more common than in the general population [51]. The ratio of squamous cell carcinoma to basal cell carcinoma in the population is approximately 1:4, and the ratio of patients after HTx, by contrast, is 4:1 [48]. Squamous cell carcinoma is more severe in transplanted heart patients than in the general population; in addition, HTx patients have a higher risk of developing primary multiple cancer, risk of metastasis, perineural and lymphatic invasion, and local recurrence due to infectious diseases, especially infection with HPV [51, 52]. Patients with squamous cell carcinoma have a higher incidence of solar keratosis [52]. Another common skin cancer is melanoma, which occurs mostly in patients with fair skin, light hair and eyes, and a tendency to freckles. Heart recipients have a 1,633-fold increased risk of melanoma, and the prognosis of the disease is poor because of the development of long-term metastases [52].

The incidence of Kaposi sarcoma is much higher in patients who have had HTx, also higher than in the general population [48] with incidence rates ranging from 0.41% to 1.2% [53]. Herpes virus infection and the effect of immunosuppressive therapy have been cited as reasons for the increased incidence [49]. About 60% of

Kaposi sarcoma cases were nonvisceral (98% were skin tumors, 2% were oral or oropharyngeal tumors), and the remaining 40% were visceral – most often affecting the gastrointestinal tract, lungs, and lymph nodes. The prognosis for Kaposi sarcoma is poor, with a median survival of 23.6 months after diagnosis. Death occurs either directly from the disease progression or as a result of acute graft rejection [54].

Lymphoproliferative disease is the second most common cancer in HTx recipients [56] and the most common disease in pediatric heart transplant recipients [55]. Most cases occur within 1 year of HTx [44], the incidence in patients after HTx ranges from 1.5% to 11.4% [56], which is higher than in other organ recipients, and it is independent of factors such as age and gender, and does not increase over time, unlike other types of cancer [57, 58]. Epstein–Barr virus infection plays an important role in the pathogenesis of lymphoproliferative diseases, so their incidence remains high for 5 years after HTx [12, 59].

Lymphoproliferative diseases after solid organ transplantation are potentially malignant complications, affecting about 1% of recipients [60]. In contrast to the general population, the development of lymphoproliferative disease in HTx recipients affects not only the lymph nodes but also the liver, lungs, central nervous system, intestines, kidneys, and spleen. Gastrointestinal and respiratory organs are the most common target organs in pediatric heart transplant recipients [61]. Although lower doses of immunosuppressants are sufficient to achieve remission in some patients, most require rituximab and/or chemotherapy. Patients with relapsed lymphoma have a poor prognosis and require treatment with new drugs, such as PD-1 monoclonal antibody inhibitors nivolumab, pembrolizumab, or atezolizumab [62].

Solid tumors are relatively rare compared to skin tumors and lymphomas, but the prognosis for these diseases is also significantly worse than for skin tumors and lymphomas. The most common post-HTx solid organ cancer is lung cancer. The most important risk factor for its development, along with immunosuppressive therapy, is old age [63]. Non-small cell lung cancer is the most common type of lung tumor seen after heart transplantation, but there are also reports of mesothelioma and carcinoid tumors [55, 56, 64]. According to Goldstein et al. [56], the average interval from HTx to diagnosis of lung cancer, is 35.7 months. The prognosis for lung cancer patients depends on the stage, and is poor in the later stages of the disease. The main reasons of such high mortality include late detection, metastasis, and rapid tumor growth [65].

As for malignant tumors of other solid organs, the incidence of prostate and bladder cancer, according to a single-center study from the United States, is 0.79% [56]. Bladder malignancies have been shown to be among the most aggressive in cardiac transplant patients, with a higher incidence than in the general population. Continued smoking after transplantation, high blood levels of testosterone, and sexual activity are important risk factors. Adenocarcinoma is the most common type of prostate cancer [65]. The median interval between transplantation and tumor diagnosis is 36.5 months, and the median survival after diagnosis and treatment is 27 months. The leading cause of death in prostate cancer is metastasis to remote organs and tissues [55].

Salivary gland tumors are usually late in detection, extremely aggressive, and metastasize early [56, 65]. Adenocarcinoma is another frequent type of gastric and intestinal cancer in HTx recipients. Tumors of this type are also prone to rapid metastasis [55].

Renal cell cancer, breast and pancreatic adenocarcinomas, liver cancer, cervical cancer, and cholangiocarcinoma of the biliary tract are rarer types of malignancies seen after HTx [66].

CONCLUSION

The risk of malignant tumors of various localizations is significantly higher in heart recipients than in the general population. This is associated with immunosuppressive drugs, smoking, and patient age. Timely comprehensive examination of patients, development of new immunosuppression regimens, treatment of infections predisposing to the development of malignant tumors, and avoiding bad habits will help to reduce the risk of malignant tumors, enable diagnosis of complications at early stages, and thereby increase the life expectancy of recipients.

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