NON-MELANOMA SKIN CANCER IN RENAL TRANSPLANT RECIPIENTS: DO WE STILL OVERLOOK IT?

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Non-melanoma skin cancer (NMSC) is the most frequent cancer in renal transplant recipients (RTRs). Clinical and epidemiological studies indicate that long-life immunosuppressive therapy that is essential for preventing graft rejection and obtaining adequate graft function after renal transplantation, combined with older age at transplantation, total sun burden during life, fair skin type and personal history of treated NMSC before transplantation, are the most important risk factors for NMSC development. Since RTRs are more susceptible to developing more aggressive types of skin cancers, especially squamous cell carcinoma (SCC), it is of great importance to develop cancer awareness in these patients, making them sensitive to sun protection and regular dermatologic and skin self-examination. Immunosuppressive therapy as a risk factor of high importance has to be individually tailored and, if necessary, altered in order to decrease cancer formation as much as possible, while preserving graft survival and function. Therefore, interdisciplinary approach, including primarily nephrologists and dermatologists, should be employed in follow up of RTRs, thus enabling prevention, early diagnosing and appropriate treatment of NMSC in these patients.

Key words: renal transplantation, immunosuppression, skin cancer, epidemiologic studies

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INTRODUCTION

Renal transplantation is nowadays established as the best therapeutic approach for end-stage renal failure, enabling patients to abandon chronic dialysis and to get prolonged life span and better quality of life. After transplantation, patients require lifelong immunosuppressive treatment which prevents graft rejection, but also increases the risk of various complications including opportunistic infections and malignancy development[(1)]. Additionally, there is increased mortality for a given stage and grade of malignancy compared with patients not receiving immunosuppressants.

It has been estimated that organ transplant recipients (OTRs) have a three- to six-fold increased risk of developing solid organ cancer or internal malignancy compared to the normal population[2]. Non-melanoma skin cancer (NMSC) is the most common cancer in renal transplant recipients (RTRs). Other malignant skin tumors such as malignant melanoma, Kaposi's sarcoma, Merkel cell cancer, sebaceous carcinoma and cutaneous lymphoma occur less frequently in RTRs, but still at a greater frequency than in the non-immunosuppressed populations[(3)].

EPIDEMIOLOGY

Several studies indicate that up to 40% of OTRs develop precancerous skin growths such as actinic keratosis and Bowen's disease (squamous cell carcinoma in situ), as well as NMSC within the first 5 years after trans-

plantation[4]. NMSC develops most frequently, accounting for 90% of all skin cancers in OTRs[5]. It is well established that immunosuppressed patients develop NMSC more often and much earlier than immunocompetent people[2]. Furthermore, it has been estimated that immunosuppressive therapy carries a 65-fold increased risk of squamous cell carcinoma (SCC) and 10 to 16-fold increased risk of basal cell carcinoma (BCC) development compared to immunocompetent population[6]. These data show that the risk of BCC increases linearly, whereas the risk of SCC increases exponentially.

The incidence of skin cancer among RTRs has been differently estimated, varying from 2% to 30%[3,7-11]. These differences could probably be ascribed to different amount of sun exposure in different populations. Most studies indicate that SCC is predominant to BCC in RTRs, with an SCC/BCC ratio of 3:1, which is reversed compared to the normal[10,12-14]. However, a minor number of studies found BCC to be the most common carcinoma in RTRs[7,15,16], which is consistent with data in the general population[17]. In addition, some authors found similar frequency of both (SCC/BCC ratio 1.1:1)[18].

RISK FACTORS

Remarkable advances in immunosuppressive therapy have led to longer survival of RTRs, which is associated with an increased risk of developing more aggressive skin cancers. Therefore, there is an urgent need to identify patients that are at the greatest risk of aggressive (metastatic) skin cancer.

Several risk factors have been identified to contribute to actuating cutaneous carcinogenesis in RTRs, including age, overall UV exposure, Fitzpatrick skin type, personal history of previous non-melanoma skin cancer and immunosuppressive therapy. The cause of renal insufficiency, HLA mismatch, blood type or RH factor do not seem to influence cancer formation[9,16], nor does the pretransplant dialysis period[9].

AGE

Older age at transplantation has been found as a risk factor for NMSC development in RTRs[12,14]. In the RTRs transplanted after age 55, the risk ratio for NMSC was 12-fold higher than in RTRs that were younger than 34 at the time of transplantation. This increasing prevalence in older age can be explained by the higher cumulative UV dose, an important risk factor for SCC development, in both immunocompetent and immunosuppressed population. Consistent to these data is the finding that OTRs that had been transplanted at the age of approximately 40 years developed skin tumors within a mean of 8 years, whereas ORTs that were older than 60 at the time of transplantation developed skin tumors within a mean of 3 years. This can be explained by the higher incidence of preclinical skin tumors in older age, which are additionally promoted by immunosuppressive therapy.

ULTRAVIOLET RADIATION

In the general population, the major risk factor for BCC development is intensive sun exposure in childhood and adolescence, while for SCC chronic cumulative sun exposure and ultraviolet (UV) cell damage is assumed[17]. Consistently, in RTRs UV exposure is also considered to be an important risk factor for NMSC development. SCC in RTRs is mostly located on sun exposed body areas such as the face, ears and hands, supporting the UV damage being a risk factor[19]. Namely, UV rays together with immunosuppressants alter skin immunity, which leads to the absence of recognition of tumor antigens and tumor initiation.

FITZPATRICK SKIN TYPE

Up to 89% of RTRs with NMSC have been classified by Fitzpatrick into type I, II or III[13]. The risk ratio for cutaneous SCC in OTRs with Fitzpatrick skin type I-II has been estimated to be 65-fold to 250-fold higher when compared with immunocompetent population[20-22].

PERSONAL HISTORY

Immunocompetent patients who develop NMSC have a 10-fold increased incidence of subsequent NMSC development (3-year cumulative risk for development of second NMSC is 18% for SCC and 44% for BCC) comparing to people who do not have personal history of NMSC23. It has been estimated that RTRs with one NMSC have a 49-times higher risk of subsequent cancer formation compared to the matched control group[24]. Usually, SCC arises in so called “field cancerization”, an area of previous great actinic damage and epidermal dysplasia. Therefore, RTRs who developed one SCC will carry a greater risk of subsequent skin cancer formation, already taking into consideration the burden of immunosuppression. Prior use of biologic therapy or a history of leukemia or lymphoma carries an additional risk of NMSC development in RTRs[19].

IMMUNOSUPPRESSIVE THERAPY

The risk rate for NMSC development in OTRs is strongly related not only to the intensity and duration of immunosuppression, but also to the type of immunosuppressive therapy. Induction therapy is introduced before, at the

time of, or immediately after transplantation induction. It includes biologic agents such as lymphocyte-depleting agents or interleukin-2 receptor agonist (IL2-RA). In heart transplant recipients, it has been shown that induction therapy consisting of antithymocyte globulin, OKT3 or monoclonal anti-IL-2 receptor antibodies carries an increased risk of NMSC development[25]. Initial and long term maintenance immunosuppressive therapy is introduced primarily to prevent acute graft rejection and to obtain adequate graft function. Introduction of calcineurin inhibitors Cyclosporin A and tacrolimus to the former double immunosuppressive protocol consisting of prednisone and antiproliferative drug (azathioprine and mycophenolate mofetil) has ameliorated graft survival. However, posttransplant cancer formation is the major problem connected to long and aggressive immunosuppression.

All immunosuppressive drugs may enhance cancer development, but the greatest risk has been attributed to azathioprine and Cyclosporin A. Photosensitivity and actuated photocarcinogenesis induced by azathioprine are caused by the interaction between DNA 6-thioguanine and UVA[26,27]. There are indications that PTCH gene mutations in BCC may also be associated with azathioprine use, particularly with cancers on non-sun-exposed skin areas[28]. Laboratory experiments suggest that Cyclosporin A inhibits mitochondrial permeability transition pore (MPTP) opening and prohibits keratinocyte cell death caused by genotoxic stress, thus promoting skin cancer development. No such effects were observed with the use of mycophenolate mofetil or tacrolimus[29,30]. When comparing azathioprine, cyclosporine and tacrolimus therapy regarding the risk of NMSC development, studies are contradictory. Some authors found a higher incidence of NMSC in patients having received cyclosporine than in those treated with azathioprine or tacrolimus[31-33], whereas others found no significant difference between the patients having received cyclosporine or azathioprine therapy[14,34,35].

Additionally, studies showed that triple immunosuppressive therapy (cyclosporine, prednisone, and azathioprine or sirolimus) posed a greater risk of NMSC than dual therapy (prednisone and azathioprine or sirolimus), and that maintenance monotherapy with calcineurin inhibitor, cyclosporin A or tacrolimus, after stabilization of graft function diminished the risk of cancer development[36].

Based on the above-mentioned studies, it has been proposed that maintenance protocol should be based on mycophenolate mofetil and low-dose calcineurin inhibitor Cyclosporin A or tacrolimus, with or without prednisone. Recent evidence suggests that novel immunosuppressive therapy, mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) prevents skin cancer formation[37,38]. Even though the use of novel immunosuppressive drugs and their exact impact on skin cancer prevention is not fully established, high risk patients, patients with previous NMSC and patients with potential metastatic spread of a skin cancer may benefit from switch to the new models of immunosuppression.

PROGNOSIS OF NMSC IN RTRS

Generally, BCC grows slowly, but if untreated, it can grow to a great extent, destroying the underlying tissues down through the bone. Opposed to BCC, SCC shows a potential for metastatic dissemination. It has been estimated that 6% of immunocompetent patients with SCC have a metastatic disease, which is connected with poor long-term prognosis.

For dermatologists who deal with skin cancers and for nephrologists who are following RTRs, the ability to recognize patients with a more aggressive type of skin cancer is of great importance. There are several factors in SCC which may point to a more aggressive type of SCC. Location of cancer on the ear and lip, history of previously treated SCC, size of more than 2 cm, depth of more than 4 mm, poor cell differentiation and perineural invasion are considered to mark SCC with greatest chance of recurrence, while all these signs in combination with immunosuppression may serve as a prognostic marker for metastatic cancer spreading[39].

Sometimes, histologic findings alone are not enough. Therefore, there is a comprehensive search for a single biomarker which will be able to recognize more aggressive SCC. It is known that tumor suppressor gene p53 regulates cell response to genotoxic stress, including UV cell damage[40]. Inactivation of both p53 gene alleles promotes surviving of genetically damaged cells and thus promotes cancer formation[41]. Immunohistochemical analysis of the p53 expression pattern is being used as a marker of gene mutation and inactivation[42]. In immunosuppressed patients, a higher intensity of p53 expression pattern has been found[19]. The level of serine protease inhibitor clade A member 1's (SerpinA1 or alpha -1-antitrypsin) expression pattern was elevated in SCC of bullous epidermolysis patients. These patients develop more aggressive skin cancers as a result of mutual action of chronic skin inflammation, skin ulceration, UV exposure and immunosuppression[43]. The role of matrix metalloproteinase 7 (MMP7) in SCC progression has been suggested, as up-regulation of MMP7 has been detected in SCC[44].

THERAPY

As NMSC are most frequent cancers in RTRs, showing a tendency to more rapid progression than in immunocompentent individuals, close monitoring of these

patients, preventive measures and early treatment are mandatory. Patients should be educated, even before transplantation, about the impact of UV radiation and immunosuppression drugs on the skin, as well as about mandatory compliance with sun protection and using both protective clothes and sunscreens. Education on regular skin self-examination is as important as dermatological follow up.

Actinic keratoses and small and superficial SCC should be early and aggressively treated by cryotherapy, topically with 5-fluorouracil cream, imiquimod cream or photodynamic therapy in order to prevent progression to invasive SCC. Lesions suspected of transition to invasive SCC should be biopsied as early as possible and treated. Although electrodesiccation and curettage may achieve acceptable curative rate, surgical excision with clear margins is more advisable. Mohs' micrographic surgery is appropriate for high risk areas. If surgical excision is not curative, adjuvant radiation therapy may be performed. Whether sentinel lymph node biopsy (SLNB) is a mandatory procedure in high risk patients or just close lymph node monitoring is sufficient, is still being debated, especially as there are no clear criteria for SLNB enrolment[24].

High risk patients, including those with metastatic SCC and patients who develop multiple SCCs (5-10 per year) may benefit from adjuvant systemic retinoid therapy. Retinoid use is both chemoprotective and serves as adjuvant therapy, but cannot replace monitoring and surgical treatment. Retinoid therapy is usually life-long, as recurrences have been observed after drug discontinuation[19].

When chemoprotection and sun protection methods are not enough or are contraindicated, switch to a different immunosuppressive regimen is preferred.

CONCLUSION

Renal transplantation promotes longer and prosperous life of patients with chronic renal failure. Chronic immunosuppression needed for graft survival goes along with complications such as infection and cancer development, with skin SCC being the most frequent one. Stronger and longer duration of immunosuppression, combined with older age at transplantation, UV radiation, fair skin color and history of NMSC before transplantation contribute to skin SCC development. Moreover, SCC in RTRs carries a tendency to aggressiveness and higher morbidity and mortality than in immunocompetent patients. RTRs should be educated about the increased risk of cancer development, the importance of skin self-examination and need for early detection, diagnosis and initiation of appropriate treatment. Therefore, interdisciplinary approach to these patients is recommended, bringing together nephrologists and dermatologists, surgeons, pathologists and oncologists. Interdisciplinary cooperation together with further scientific advances in the fields of transplantation and dermato-oncology should help us identify the group of RTRs with a tendency of developing invasive SCC, so that they can be put under more regular and careful supervision.

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SAŽETAK

NEMELANOMSKI KARCINOM KOŽE U PRIMATELJA BUBREŽNOG PRESATKA – PROPUŠTAMO LI TO JOŠ UVIJEK?

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Nemelanomski karcinomi kože najčešći su karcinomi u bolesnika s transplantiranim bubregom. Kliničke i epidemiološke studije ukazuju na to da su najvažniji čimbenici rizika za razvoj nemelanomskih karcinoma kože doživotna imunosupresivna terapija nužna za sprječavanje odbacivanja presatka i održanje njegove funkcije te starija životna dob bolesnika prilikom transplantacije, izloženost UV zrakama tijekom života, svjetliji tipovi kože i osobna anamneza preboljelog karcinoma kože prije transplantacije. Budući da su bolesnici s transplantiranim bubregom skloniji razvoju agresivnijih tipova kožnih karcinoma, osobito planocelularnog karcinoma, izrazito je važno razviti svijest bolesnika s transplantatom o povećanoj sklonosti razvoju karcinoma kože, potrebi za prevencijom te redovitim dermatološkim pregledima i samopregledima kože. Imunosupresivnu terapiju treba prilagoditi svakom pojedinom bolesniku te ju po potrebi modificirati kako bi se smanjio rizik za pojavu karcinoma uz istodobno održanje funkcije presatka. Za praćenje bolesnika s transplantiranim bubregom potreban je interdisciplinarni pristup uključujući primarno nefrologe i dermatologe kako bismo omogućili bolesnicima s transplantatom prevenciju, ranu dijagnozu i odgovarajuće liječenje karcinoma kože

Ključne riječi: transplantacija bubrega, imunosupresija, karcinomi kože, epidemiološke studije