VERSITA

Cent. Eur. J. Med. • 8(3) • 2013 • 322-327
DOI: 10.2478/s11536-012-0132-7

Central European Journal of **Medicine**

Malignancies after kidney transplantation: 3 clinical case reports

Case Report

Eglė Dalinkevičienė[1]*, Vytautas Kuzminskis[1] Laura Kairevičė[2], Rasa Jančiauskienė[2], Daimantas Milonas[3], Mindaugas Jievaltas[3], Birutė Sribikienė[1], Inga-Arūnė Bumblytė[1]

1 Department of Nephrology, Medical Academy, Lithuanian University of Health Sciences, Lithuania

2 Department of Onco-haematology, Medical Academy, Lithuanian University of Health Sciences, Lithuania

3 Department of Urology, Medical Academy, Lithuanian University of Health Sciences, Lithuania

Received 24 July 2012; Accepted 27 December 2012

Abstract: Post-transplant malignancies present an aggressive course and are a significant cause of morbidity and mortality. Tumours of viral ethiology have the greatest risk in renal transplant recipients. Oncogenic effect of immunosuppressive therapy is another major risk factor of post-transplant malignancy. We report cases of three different types of malignancies developed after kidney transplantation: non-Hodgkin's lymphoma, Kaposi's sarcoma and germ cell testicular cancer (nonseminoma).

Keywords: *Kidney transplantation • Malignancy • Non-Hodgkin's lymphoma • Kaposi's sarcoma • Germ cell testicular cancer (nonseminoma)*

1. Introduction

Transplant patients have a higher incidence of malignancies, and the types of them are different to compare with general population [1-3]. The relative risk of malignancies ranges from 2-3 fold increase for common malignancies (lung, prostate, breast, colon) to a 100- fold increase for nonmelanomatous skin cancers, lymphomas and Kaposi's sarcoma [1-7]. Comparison with hemodialysis patients shows 10-times higher risk of malignancy in transplantated patients [8,9]. The cumulative prevalence of malignancy increases with the duration of follow-up [10].

2. Case 1

A 41- year-old man, with a 3-year history of hemodialysis, received a cadaveric renal transplant in January 2010. The cause of end – stage renal disease was bilateral hypoplastic kidneys. The post-transplant period was uneventful and graft function was excellent. Immunosuppression consisted of cyclosporine (150 mg; the serum cyclosporine level was in the range of 90-115μg/l), azathioprine (50 mg) and methylprednisolone (8 mg). Ten months after transplantation, the patient was presented to outpatient department complaining of general weakness, loss of appetite and decrease of weight. On physical examination, his weight was 50 kg, and BMI 17,3 kg/m^2. Laboratory investigation showed good graft function (serum creatinine 78 μmol/l) and slight hypoproteinemia (total protein 55 g/l, serum albumin 33 g/l). Gastroscopy revealed only few erosions in antral part. Chest x-ray showed no pulmonary opacities. Abdominal ultrasound revealed hypoechogeneous multiple lesions in the right lobe of the liver, suggestive metastatic lesions.

The patient was admitted to nephrology department for further assessment. Computerized tomography (CT) of the abdomen confirmed the presence of multifocal

* *E-mail: egle.dalinkeviciene@gmail.com*

nodules (0,2-2,1 cm) in the liver and spleen and 1,4x1,5 cm hypodense node in transplanted kidney, typical to metastatic changes. The liver biopsy was performed. Histological evaluation revealed several polymorphic infiltrates, consisting mainly of medium-sized lymphoid cells positive for CD20, BCL-2, negative for CD3 (positive for small T lymphocytes), BCL-6, CD10, Cyclin D1 (Figure 1, A, B and C). The diagnosis of diffuse large B-cell lymphoma was confirmed. After that, immunosuppression was reduced: azathioprine was stopped, dose of cyclosporine was reduced by half (75 mg). Methylprednisolone dose (8 mg) was left unchanged. The treatment of lymphoma consisted of 8 cycles of R-CHOP chemotherapy in standart dosage (rituximab + doxorubicin + cyclophosphamide + vincristine + methylprednisolone). After chemotherapy, the metastatic nodular lesions in the liver, spleen and transplant kidney disappeared. Graft function remained normal. With the aim to minimize the risk of malignancy recurrence, immunosuppression scheme was changed: cyclosporine was switched to sirolimus and mycofenolate mofetil was appointed instead of azathioprine. The patient is under the follow-up by nephrologist and oncologist. One year after lymphoma treatment, no malignancy recurrence was observed.

3. Case 2

A 57-year-old man,with end-stage renal disease secondary to hypertensive nephropathy, was on maintain haemodialysis for 5 years. At the end of 2009, he received a cadaveric renal transplant. Immunosuppressive therapy included cyclosporine (250 mg; serum cyclosporine level was in the range of 98-120 µg/l), mycofenolate mofetil (2g) and methylprednisolone (6 mg). The graft function was satisfactory (serum creatinine 200 µmol/l). Fourteen months after transplantation, a skin rash had occurred in the legs (Figure 2, A, B and C). The patient was referred to dermatologist and skin biopsy was performed. Very soon after that, hydronephrosis and pyelonephritis developed in transplanted kidney. Graft function deteriorated significantly (serum creatinine 721 µmol/l), requiring few sessions of haemodialysis. The patient was referred to urologist and nephrostoma was performed, graft function improved. At that time, results of skin biopsy were obtained (Figure 3, A and B). Histology revealed Kaposi's sarcoma. The sonography of the abdomen showed conglomerates of enlarged inguinal lymph nodes. Immunosuppression was reduced: mycofenolate mofetil was stopped, dose of cyclosporine was reduced by half (125 mg), methylprednisolone continued unchanged (6 mg). Treatment of Kaposi's sarcoma was started with doxorubicin 15mg/m². Few days later, pyelonephritis developed again in transplanted kidney with severe graft dysfunction (serum creatinine 1135 µmol/l). Haemodialysis was restarted. Treatment with antibiotics was ineffective, septic complications progressed. CT scan revealed abscess in transplanted kidney, extension of infiltration to surrounding graft tissue, and pelvic blood vessels. CT scan showed also multiple enlarged lymph nodes in the

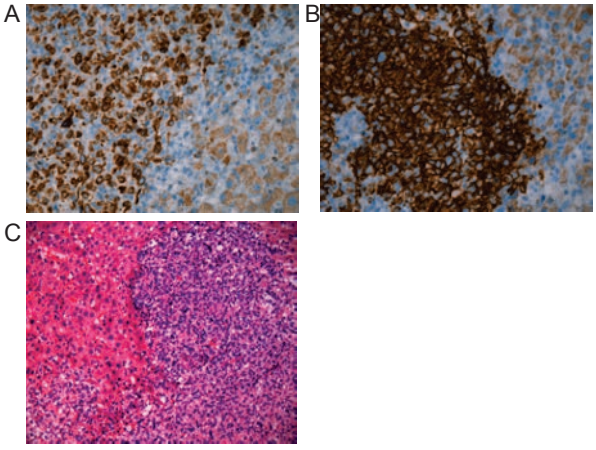

Figure 1. (A) Immunohistochemistry stain showing lymphoid cells positive for BCL-2 (magnification 400x), (B) lymphoid cells positive for CD20 (magnification 400x), (C) Hematoxylin-eosin (HE) stain showing lymphoma cells (magnification 200x).

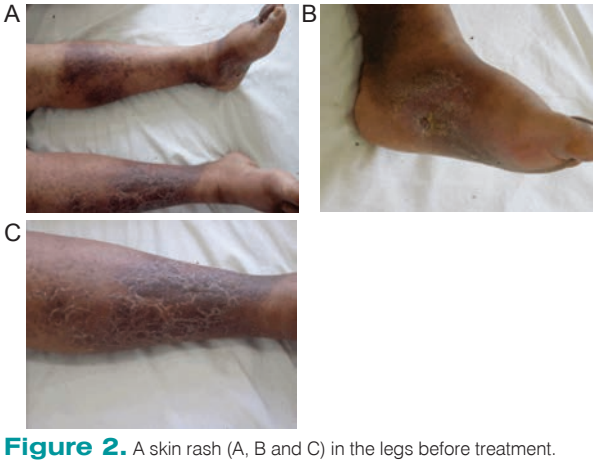

Figure 2. A skin rash (A, B and C) in the legs before treatment.

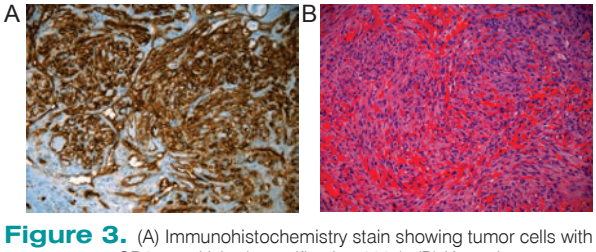

Figure 3. (A) Immunohistochemistry stain showing tumor cells with CD34 positivity (magnification 200x), (B) Kaposi sarcoma (skin tumor cells) in HE stain (magnification 200x).

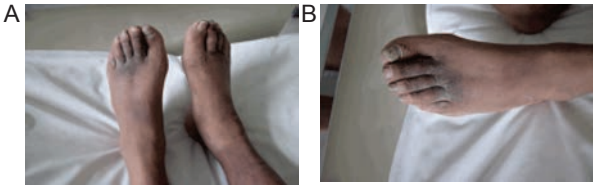

Figure 4. Extensive regression of Kaposi sarcoma after treatment (A and B), he only has hyperpigmented areas at knee levels, skin looks thin and delicate and easily bruised.

abdomen and pelvis. Because of life-threatening infection complications, it was decided to stop completely immunosuppression and to remove transplanted kidney. After graft nephrectomy, chemotherapy with doxorubicin was renewed. Following 3 cycles of chemotherapy, skin rash in the legs disappeared (Figure 4, A and B) and size of lymp nodes decreased. One year later after sarcoma treatment, the patient is doing well on ambulatory haemodialysis.

4. Case 3

A 25-years-old man had a renal graft transplantation in 2007 due to chronic glomerulonephritis. Postoperative immunosuppressive therapy consisted of cyclosporine (225 mg), azathioprine (75 mg) and methylprednisolone (4 mg). The serum cyclosporine level (95 µg/l) was stable. Three years after transplantation, he noticed the enlargement of left testicle. Ultrasound of left testicle revealed increased testis with 2x2 cm hyperechogenic area inside. Preoperative human chorionic gonadotrophin (hCG) was 1900 U/l (normal values 0-5 U/l), alpha fetoprotein (AFP)- 2491,9 kU/l (normal values 0-7.89 kU/l), LDH- 1179 U/l (normal values 0- 248 U/l). In case of testicular malignancy suspicion, at 11/2010 left orchofuniculectomy was done. Morphological analysis confirmed mixed germ cell tumour: 95% of tumor mass was embryonal carcinoma and 5% mature teratoma, pT3 Nx Mx, R1. CT scan of chest, abdomen and pelvis (12/2010) revealed multiply small metastases in both lungs (Figure 5, A and B), pathological lymph nodes in posterior mediastinum (Figure 5, C), conglomerates of multiply pathological paraaortic lymph nodes (Figure 5, D) and metastasis in transplanted kidney (Figure 5, E).

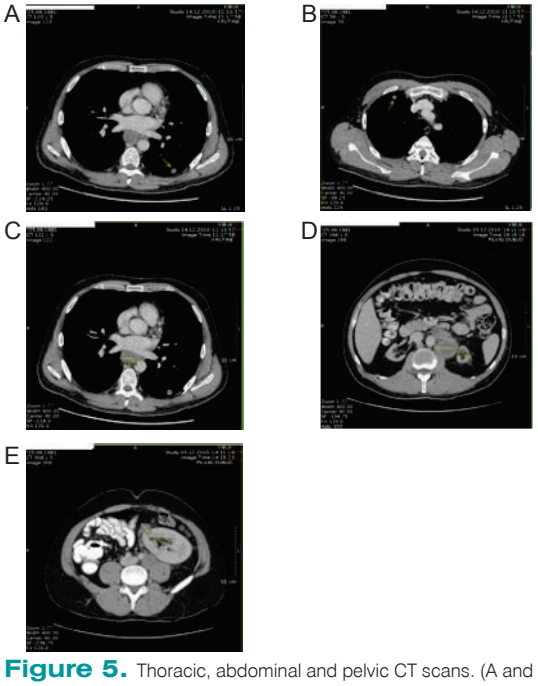

Figure 5. Thoracic, abdominal and pelvic CT scans. (A and B) Multiply small 0.2 – 0.9cm in diameter metastases in both lungs. (C) Pathological 3.7x 2.7cm lymph nodes in posterior mediastinum. (D) Conglomerates of multiply pathological paraaortic lymph nodes. (E) Metastasis in transplanted kidney.

We decided to start chemotherapy with 4 cycles of carboplatin (instead of cisplatin), etoposide, and bleomycin every 3 weeks. Doses of chemotherapy agents were reduced by 25%. Also prophylactic granulocyte colony-stimulating factors (G-CSF) were added after each chemotherapy cycle. Chemotherapy doses: carboplatin AUC 6 i.v. day 1 (350 mg); Etoposide 100 mg/m^2 i.v. day 1-5 (in total 720 mg for one cycle); Bleomycin 30 mg i.v. day 1, 8 and 15. Bleomycin was omitted at first cycle day 1 and day 15 (latter due to febrile neutropenia, trombocytopenia, anemia); at cycle 2–day 1 and day 15 (latter due to trombocytopenia); at cycle 3–day 15 (due to trombocytopenia); at cycle 4–day 15 (due to febrile neutropenia, trombocytopenia and anemia).

Renal function remained stable with creatinine ranges in 169-104-150 mcmol/l during all treatment period. Immunosuppression with cyclosporine (225 mg) and methylprednisolone (4 mg) was continued, azathioprine

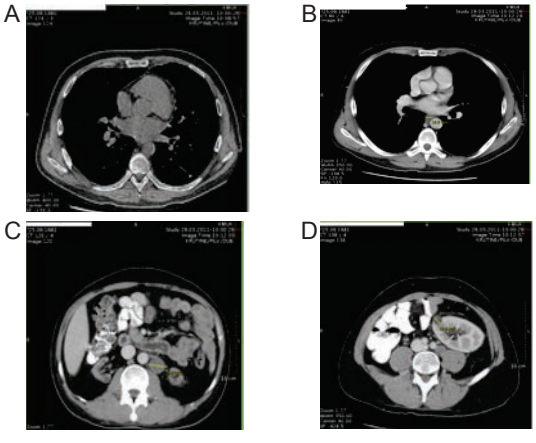

Figure 6. Residual masses of tumor after chemotherapy. (A) Left lung S6 metastasis. (B) No signs of pathological lymph nodes in posterior mediastinum. (C) Pathological paraaortic lymph nodes. (D) Metastasis in transplanted kidney.

was omitted. Febrile neutropenia, also anemia, thrombocytopenia requiring blood components transfusions occurred after 1st and 4th chemotherapy cycles. After completion of 4 chemotherapy cycles, tumor markers decreased up to normal range (AFP-2,8kU/l, HCG-0,3U/l, LDH-213 U/l). Following the guidelines of the treatment, we decided to remove all residual masses of tumor (Figure 6, A, B, C and D–residual masses of tumor after chemotherapy, yellow lines).

Follow up visits were every 2-3 months. Until 02/2012- no signs of tumor progression: tumor markers were in normal ranges; chest, abdominal and pelvic CT showed no metastasis or pathological lymph nodes. Patient's performance status was good. Renal graft function was in adequate values.

5. Discussion

Malignancy is the third major cause of death in kidney transplant recipients (first two are cardiovascular diseases and infections) [9,11,12]. The main risk factors of post-transplant malignancy are immunosuppression and oncogenic virus. They both induced tumors after kidney transplantation. Immunosuppresion can accelerate the occurrence of cancer. [7,13-15]. We reported 2 cases of post-transplant malignancy, associated with viral infections. First case is B-cell lymphoma (non–Hodgkin's). This lymphoproliferative disease is related to Epstein–Barr virus (EBV) [16]. Seronegative recipients which receive an organ from a seropositive donor are at highest risk. Anti-lymphocyte antibodes (ATG, OKT3) or large doses of cyclosporine or tacrolimus and azathioprine also increase the risk [17–20]. EBV transforms B-lympocytes and promote uncontrolled proliferation [16,20,21]. In our case, lymphoma developed within first year after kidney transplantation and presented with lymphadenopathy and extranodal involvement of liver, spleen, graft. It presented a typical course of disease. Significant reduction of immunosuppression and treatment with rituximab and conventional chemotherapy (CHOP) reversed the process. Graft function remained in normal value. To reduce malignancy reccurency, cyclosporine was changed to sirolimus and azathioprine to mofetil mycofenolate. Some clinical evidence suggests that the incidence of post-transplantation malignancy is lower in patients receiving sirolimus or everolimus than in patients receiving other immunosupressive therapies [5,22,23]. Mammalian Target of Rapamycin (mTOR) inhibitors presents antineoplastic effects by direct inhibition of cancer cell replication, by induction of apoptosis and inhibition of IL-10, vascular endothelial growth factor (VEGF) production and inhibition of angiogenesis [24,25]. MMF also may have a protective effect against malignancy. Some studies indicated an antitumor effect against colon and prostate cancer cells, others found MMF to be associated with a decrease in the relative risk of developing post-transplant lymphoproliferative disorder (PTLD) compared to AZA [24]. Antiviral agents were not given to our patient with lymphoma as they are not recommended. Few studies have examined outcomes after lymphoma diagnosis. They found that posttransplant lymphoma is associated with a 17-fold increased risk of death due to disease complications [26].

The second case is Kaposi's sarcoma, related to Human Herpesvirus-8 (HSV-8). It presented 14 months later after kidney transplantation with macular skin lesion and later disseminated to lymphnodes. According to the literature, in 40 percent of cases the clinical course is aggressive with involvement of visceral organs, and may respond to reduction of the doses of immunosuppressive agents what leads to complete remission in 30 percent of the patients [27]. Others recommend to switch to sirolimus, but sometimes chemotherapy or radiotherapy are required [6]. The use of sirolimus in place of ciclosporin has been associated with complete regression of Kaposi's sarcoma in renal transplant recipients [28,29]. In our case we stopped immunosuppression and removed the graft because of infection complication (abscess) in transplanted kidney. Haemodialysis was started and treatment with doxorubicin was given after what skin rash disappeared and lymphnodes decreased. The second line monochemotherapy is etoposide, vinblastine, doxorubicin, bleomycin and vincristine or combinations of these drugs [30,31].

The third our report is about very rare case of post-transplant malignancy. There are little literature data on metastatic testicular germ cell cancer after renal transplantation. Germ cell testicular tumors account for only 1.7 % of all de novo cancers after renal transplantation [32]. According to clinical experience in medical literature it is recommended to choose standard chemotherapy with cisplatin [32] or carboplatin [33], etoposide, bleomycin [32]. Dose reduction could be up to 25-50% and close monitoring of renal function is mandatory. Also prophylactic GCSF for febrile neutropenia prevention is recommended. It is also recommended before chemotherapy discontinue azathioprine while leaving cyclosporine and glucocorticoids for immunosuppression [32]. Some authors suggest switching cyclosporine to sirolimus, which presents antiproliferative, antineoplastic effect [5,7]. Our patient developed germ cell testicular malignancy with multiply metastasis 3 years after kidney transplantation. We started with chemotherapy with reduced doses of carboplatin and etoposide only

by 25% while keeping full doses of bleomycin. We realized full complex treatment with GCSF prophylactic which led to tumor regression following tumor masses resection from transplanted kidney, left lung and retroperitoneal lymph nodes. Graft function remained in adequate values. Immunosuppression was continued with sirolimus (instead of cyclosporine), mycofenolate mofetil and methylprednisolone.

Early diagnose and treatment of posttransplant malignancies is very important. Preventive strategies and detecting of malignancies in the transplant patients relies upon periodic examinations and strict adherence to prophylactic measures. Specific problems relating to screening of malignancies after kidney transplantation are discussed in the American Society of Transplantation (AST) Clinical Practice Guidelines and European Best Practice Guidelines [34,35]. Guidelines recommends for liver cancer screening to monitor liver function tests with routine lab work, ultrasound of abdomen every 6-12 months, in presence of hepatitis C or B to check alpha-fetoprotein every 6-12 months, for cervical cancer screening – annual Pap smear and pelvic exam, especially in HPV+, for breast cancer- yearly mammogram for women over 40 years old, for prostate carcinoma-yearly rectal exam and PSA [34,35].

In preventive of malignancies is important not only careful screening of the kidney recipients but the donors also. It helped to prevent underlying preexisting malignancies in donors. Today we have available abundant information in regard to transmission risk of donor-recipient tumor thanks to registries such as Israel Penn Transplant Tumor Registry [36], United Network for Organ Sharing Registry [37], The Spanish National Transplant Organization (ONT) Tumor Registry [38] and others. Transmission of a tumor from donor to the recipients is rare [36,38], but we cannot forget that the risk exists. Malignant melanoma, choriocarcinoma, lymphoma, carcinoma of the lung, breast, colon, renal cell cancer belong to malignancies with an increased risk of donor to recipient transmission [36].

6. Conclusions

This report highlights the importance of cancer screening after renal transplantation. The screening shoud not be limited only to common malignancies as limphoproliferative disease, Kaposi sarcoma, skin cancer. One from our three reported cases was very rare embrional testicular carcinoma. Early diagnosis and treatment of posttransplant malignancies were successful in our patients. Preventive strategies as control of oncogenic virus must be implemented after transplantation in an attempt to reduce the development of malignant tumors.

Statement of Conflicts of Interest

The authors state no conflicts of interest.

References

[1] Sheil AG, Disney APS, Mathew TH, et al. De novo malignancy emerges as a major causes of morbidity and late failure in renal transplantation. Transplant Proc 1993;25:1383

[2] Peto J. Cancer epidemiology in the last century and the next decade. Nature 2001;411:390–395

[3] Birkeland SA, Lokkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. Lancet 2000;355:1886–1887

[4] Zeier M, Hartschuh W, Wiesel M, Lehnert T, Ritz E. Malignancy after renal transplantation. Am J Kidney Dis 2002;39:E5

[5] Wimmer CD, Rentsch M, Crispin A, et al. The janus face of immunosuppression – de novo malignancy after renal transplantation: the experience of the Transplantation Center Munich. Kidney Int. 2007;71:1271–1278

[6] Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am. J. Transplant. 2004;4:905–913

[7] Morath C, Mueller M, Goldschmidt H et al. Malignancy in renal transplantation. J Am Soc Nephrol 2004;15:1582–1588

[8] Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for endstage renal disease: an international collaborative study. Lancet 1999;354:93–99

[9] Briggs JD. Causes of death after renal transplantation. Nephrol. Dial. Transplant.2001;16:1545–154

[10] Yang TC, Shu KH, Cheng CH, Wu MJ, Lian JD. Malignancy following renal transplantation. Zhonghua Yi Xue Za Zhi (Taipei) 1998;61:281–288

[11] Howard RJ, Patton PR, Reed AI, et al. The changing causes of graft loss and death after kidney transplantation. Transplantation 2002;73:1923–1928

[12] Collins AJ, et al. Excerpts from the United States Renal Data System 2003 Annual Data Report: atlas of end-stage renal disease in the United States. Am J Kidney Dis. 2003;42(5):S1–S230
[13] Miao Y, Everly JJ, Gross TG, Tevar AD et al. De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. Transplantation 2009;87:1347–1359
[14] Kauffman HM, Cherikh WS, McBride MA et al. Posttransplant de novo malignancies in renal transplant recipients: the past and present. Transpl Int 2006; 19:607–620
[15] Caillard S, Dharnidharka V, Agodoa L et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005; 80:1233–1243
[16] Liebowitz, D. Epstein–Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. N Engl J Med. 1998; 338:1413–1421
[17] Opelz G, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004;4:222–230
[18] Dantal J, Hourmant M, Cantorovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomized comparison of two cyclosporin regimens. Lancet 1998;351:623–628
[19] Kirk AD, Cherikh WS, Ring M, et al. Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. Am J Transplant. 2007;7: 2619–2625
[20] Schmidtko J, Wang R, Wu CL, et al. Posttransplant lymphoproliferative disorder associated with an Epstein-Barr-related virus in cynomolgus monkeys. Transplantation 2002;73:1431–1439
[21] Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. Lancet 1993;342:1514–1516
[22] Campistol JM, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol 2006;1:581–589
[23] Kahan BD, et al. Low incidence of malignancy among sirolimus/cyclosporine-treated renal transplant recipients. Transplantation 2005;80:749–758
[24] Chapman JR,Capistol JM. Malignancy in renal transplantation: opportunities with proliferation signal inhibitors. Nephrol Dial Transplant 2007;22(I):i1-i3
[25] Gurk-Turner C, Manitpisitkul W, Cooper M. A comprehensive review of everolimus clinical reports: a new Mammalian target of rapamycin inhibitor. Transplantation. 2012;94(7):659-68
[26] Kasiske BL, Kukla A, Thomas D, et al. Lymphoproliferative Disorders After Adult Kidney Transplant: Epidemiology and Comparison of Registry Report With Claims-Based Diagnoses. Am J Kidney Dis 2011;58(6):971-980
[27] Gotti E, Remuzzi G: Post-transplant Kaposi's sarcoma. J Am Soc Nephrol 1997;8:130-137
[28] Campistol JM, Gutierrez-Dalmau A, Torregrosa JV. Conversion to sirolimus: a successful treatment for posttransplantation Kaposi's sarcoma. Transplantation 2004;77:760-762
[29] Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005;352:1317–1323
[30] Shepherd FA, Maher E, Cardella C, et al. Treatment of Kaposi's sarcoma after solid organ transplantation. J Clin Oncol 1997;15:2371-2377
[31] Brambilla L, Labianca R, Boneschi V, et al. Mediterranean Kaposi's sarcoma in the elderly: a randomized study of oral etoposide versus vinblastine. Cancer 1994;74:2873-2878
[32] Olay Dahl, Geirfinn Vagstad, Bjarne Iversen. Cisplatin-based chemotherapy in a renal transplant recipient with metastatic germ cell testicular cancer. Acta Oncologica 1996; 35:759-761
[33] Dean C, Bloomfield D, Holt S. The challenge of germ cell tumour therapy in dialysis and transplantation. Nephrol Dial Transplant. 2005;20(12):2867-2868
[34] Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, et al. Recommendations for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol. 2000;11:S1–86
[35] European Best Practice Guidelines. Nephrol Dial Transplant 2002;17(4):37
[36] Penn I. Transmission of cancer from organ donor. Nefrologia1995;15(3):205-213
[37] Kauffman HM, McBride MA, Delmonico FL. First report of the United Network for Organ Sharing Transplant Tumor Registry: donors with a history of cancer. Transplantation. 2000;70(12):1747-1751
[38] Garrido G, Matesanz R. The Spanish National Transplant Organization (ONT) tumor registry. Transplantation 2008;85(8):S61-63