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ORIGINAL ARTICLE

Bacillus Calmette-Guerin therapy in non-muscle-invasive bladder carcinoma after renal transplantation for end-stage aristolochic acid nephropathy

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Conflicts of Interest
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Summary

Intravesical instillation of bacillus Calmette-Guerin (BCG) is the treatment of choice for non-muscle-invasive bladder cancer (NMIBC) of high grade and/or carcinoma *in situ*. This study evaluated the feasibility, efficacy, and tolerance of BCG instillations in eight kidney recipients for end-stage aristolochic acid nephropathy (AAN), a condition at high risk of urothelial carcinoma, and diagnosed for NMIBC. Five of them had relapsed after mitomycin C treatment. Tolerance to BCG was evaluated clinically and regular follow-up with fluorescence cystoscopy was performed along with renal graft function monitoring. Immunosuppression doses were adjusted and prophylactic anti-tuberculous treatment given to reduce risks of graft rejection and infection. After a mean follow-up period of 50 months, seven of the eight patients are free of relapse and kidney graft function remained unchanged. Tolerance was good, except for one episode of fever and one early discontinuation because of subjective discomfort. No systemic tuberculous infection was observed. This is the first clinical observation of successful BCG therapy for NMIBC in patients given transplant for end-stage AAN. Under standardized conditions, immunotherapy based on intravesical BCG is feasible, effective, and well tolerated in renal transplantation.

Introduction

In the early 1990s, a rapidly progressive tubulointerstitial nephropathy of toxic origin was described in Belgium. This nephropathy was associated with intake of Chinese herbal root extracts containing aristolochic acid (AA) resulting in interstitial renal fibrosis and tubular atrophy [1,2]. The causative role of AA was confirmed by demonstration of specific AA-DNA adducts in the patients' renal tissue and in experimentally reproduced kidney lesions after administration of AA to rabbits and rodents [3–5]. Since the initial report, other cases have been reported worldwide, including Asia, the United States, and other European countries [6]. Plants containing AA are still in use in traditional eastern medicine (China, Taiwan, Japan, and India) and compounds containing *Aristolochia* species are still available for sale on the internet despite safety alerts published by the US Food and Drug Administration and other regulatory

agencies in the US and Europe [7,8]. AA are nitrophenanthrene derivatives, which are not only nephrotoxic but also potently carcinogenic and herbal remedies containing *Aristolochia* species were recently classified by the International Agency for Research on Cancer and the US Toxicology program as being carcinogenic for humans [9,10] (http://ntp.niehs.nih.gov). Indeed, AA nephropathy (AAN) is frequently associated with upper tract urothelial carcinoma at advanced stage after the onset of the nephropathy [11]. It may also occur in individuals with normal renal function parameters [12]. It has become clear that AAN is a global disease and that AA exposure is also the cause of Balkan endemic nephropathy (EN) [13]. Recent definitive proof of environmental AA exposure in patients with Balkan EN has come from detection of deoxyadenosine aristolactam I-DNA adducts (dA-AAI-DNA) in renal cortical and urothelial malignant tissue [14]. In Taiwan, the remarkably high incidence of upper urinary tract carcinoma was linked to the widespread use of Aristolochia herbal remedies. In their molecular epidemiologic study, Chen *et al.* [15] also reported the presence of dA-AAI-DNA in the renal cortex of patients as well as the same p53 mutational signature dominated by otherwise rare A:T to T:A transversions. Actually, studies in our Belgian cohort of AAN patients showed a very long persistence of dA-AAI-DNA in renal tissue (more than two decades), appearing as a critical determinant for the AA mutational fingerprint found in oncogenes and tumor suppressor genes recently identified [16].

In our hospital, we propose the prophylactic surgical removal of native kidneys and ureters to all patients with end-stage AAN who are receiving dialysis or undergo renal transplantation. Histological data have shown that nearly 40% of AAN patients display multifocal high-grade urothelial carcinoma, mostly in the upper urinary tract [11]. Because of this upper tract localization, bladder screening cystoscopy is proposed to all patients with AAN who undergo renal transplantation [17]. Started in 1998, this screening program consists of biannual cystoscopy, including cytological analysis and pathological examination of biopsied tissues or resected tumors. An unusually high 52% incidence of bladder cancer (BC), mostly early stage, has been found [18]. As the goals of treatment are to reduce recurrence and prevent progression to a more advanced stage, prophylactic therapeutic options are important.

Between 1998 and 2007, intravesical instillation of mitomycin C was the preferred option, because local immunotherapy using bacillus Calmette-Guerin (BCG) was considered to be contraindicated in patients with immunosuppression. However, faced with recurrent cases of carcinoma *in situ* (CIS) and following encouraging results from Palou's group in their cohort of three transplanted patients [19], we decided to offer the same therapeutic option to our AAN kidney recipients with non-muscle-invasive bladder cancer (NMIBC) at high risk of tumor progression (pT1HG or CIS).

We present our experience of the efficacy and tolerance of BCG therapy in a cohort of AAN kidney transplant recipients. We also confirm the positive impact of a long-term screening cystoscopy program on the outcome of disease and subsequent management of this high-risk patient group.

Subjects and methods

Patients

In our hospital, among the group of 105 patients diagnosed since 1992, 51 AAN patients actually reached end-stage renal failure. They have been chronically dialysed before receiving a kidney transplant 2–3 years later. As the first case of invasive multifocal urothelial carcinoma occurred on September 1997, we proposed to all our kidney recipients for end-stage AAN to undergo the prophylactic removal of native kidneys and ureters followed by bladder endoscopic examination. Except for one case of papillary bladder tumor, all cancer cases were urothelial carcinomas of the upper urinary tract [11].

Considering the high carcinogenic properties of AA, a screening cystoscopic program was set up in 1998 in our cohort of AAN kidney transplant recipients. Among 48 AAN kidney recipients enrolled in the BC screening protocol, two were lost to follow-up and three refused screening after initially having consented. Of the 43 patients who followed the screening cystoscopy program, 24 have so far been diagnosed with NMIBC, that is, 15 CIS, 5 low Grade Ta/T1, and 4 high Grade Ta/T1. None has died from BC. The three patients who declined follow-up have all died with advanced metastatic BC [18].

Between 1998 and 2007, the therapeutic approach to high-grade NMIBC (CIS and high Grade Ta/T1) consisted of transurethral resection of the bladder tumor (TURBT) followed by intravesical mitomycin C (40–60 mg/week during 6 weeks, followed by 40–60 mg/month) for 1 year as first-line therapy. Some patients moved abroad and were treated by other urologists. Among the nine patients treated in our center during the entire longitudinal follow-up period (1998–2014), two developed muscle-invasive BC: one underwent cystectomy with allograft nephrostomy and the other cystectomy with ileal conduit. Two patients received a second cycle of mitomycin C instillations because of recurrence of CIS and are still free of BC. The remaining five patients had relapses of their BC and were included in the BCG protocol that is the focus of the current study.

In this study, eight patients (54–72 years) from the Nephrology and Urology Departments of Erasme Hospital were eligible and included. All had functioning kidney

transplants, having undergone bilateral uretero-nephrectomy in the context of prior AA exposure, as attested by the detection of dA-AAI-DNA in renal tissue samples (Table 1).

During the cystoscopy screening, patients were diagnosed with non-muscle-invasive BC (pTa or pT1 high grade) or carcinoma *in situ* (CIS). They underwent transurethral resection (TURBT) and random bladder biopsies for pathological examination. On diagnosis, and after multidisciplinary consensus, patients were proposed BCG therapy. This treatment normally started with a 6-week full-dose induction course [40 mg of BCG (OncoTICE®, MSD Belgium, 1200 Brussels, Belgium)], followed by maintenance therapy, consisting of a 3-week instillation of BCG at 3 and 6 months after induction and then every 6 months for 18 months. The maintenance therapy was actually shortened or prolonged according to the histological results collected after control bladder biopsies.

Bladder follow-up

Cystoscopy with systematic biopsies was performed on the trigonal zone, with bladder cytology even if cystoscopy was normal. Biopsies and tumor resections were performed whenever cystoscopy was abnormal and when tumors were suspected. Photodynamic diagnosis-guided cystoscopy was performed using blue light after intravesical instillation of hexaminolevulinic acid (Hexvix©) to help identify tumors not visible under white light. When a bladder tumor was visible, complete resection, including the detrusor muscle, was performed to permit grading and staging. Histopathological diagnoses were reviewed by the same uropathologist (SR). Urothelial carcinomas were graded and staged according to the 2004 World Health Organization Classification of Tumors and the 2010 Union of International Cancer Classification, the TNM Classification, respectively [20,21].

Quality improvement plan

Classical maintenance immunosuppressant regimens (association of calcineurin inhibitors, azathioprine, or mycophenolate mofetil, and corticoids) were used according to standard recommendations. However, most of the patients were switched to a mammalian target-of-rapamycin (mTOR) inhibitor as there has been evidence for lower risk of new malignancies in randomized controlled trials comparing mTOR with other immunosuppressants [22–24].

Precautionary measures applied from day −1 to +1 of the instillations were antituberculous prophylaxis with nicotibine 150 mg/day, rifampicin 300 mg/day, and 250 mg twice daily of an oral fluoroquinolone (ciprofloxacin). Modification of the immuno-suppressant regimen included doubling of calcineurin inhibitors (tacrolimus or cyclosporine) or mTOR inhibitors (sirolimus or everolimus). These drugs are metabolized in the liver by cytochrome P450 3A4, which is strongly induced by rifampicin. Over time, immunosuppressant doses were reduced to decrease the risk of infection and malignancy when the risk of acute rejection decreased. The protocol included a

Table 1. Clinical characteristics of kidney transplant recipients in relation with prior aristolochic acid (AA) exposure.

Patient number	1	2	3	4	5	6	7	8
Gender/smoker*/BMI	F/0/21	F/0/29	F/(+)/22	F/(+)/27	F/0/22	F/0/23	F/0/24	F/0/22
Analgesics/NSAID †	past/0	0/0	past/+	0/0	+/+	0/0	0/0	past/0
Cumulated AA dose	308 g	126 g	358 g	220 g	184 g	162 g	226 g	204 g
Time duration of AA intake	22 months	7 months	11 months	18 months	15 months	17 months	13 months	19 months
Age at dialysis start	48 years	56 years	43 years	59 years	42 years	46 years	65 years	42 years
Age at transplant	50 years	59 years	44 years	60 years	45 years	49 years	65 years	43 years
Native pelvis and/or ureter urothelial carcinoma	CIS	CIS	CIS	CIS	pTa	None	None	CIS
dA-AAI-DNA in renal tissue (mean ± SD/10^9 nucleotides)	28.7 ± 9.2	56 ± 18.2	2.6 ± 1	13.8 ± 6.2	160 ± 50	No tissue available	50	10.6 ± 3.2
Time period from start AA exposure to bilateral nephroureterectomy (months)	95	95	90	96	99	112	167	94

CIS, carcinoma *in situ*; pTa, papillary low-grade tumour.

Patients N°1–5 and 8 are from the initial AAN patient cohort originally published in 2000 [ref 11], reporting the prevalence of upper urinary tract carcinoma.

dA-AAI-DNA: 7-(deoxyadenosine-N6-yl)-aristolactam I- DNA adduct was determined in triplicate in renal tissue samples, except for case N°7 using the nuclease P1 enrichment version of the phosphorus-32 postlabeling method [ref 3,11].

*(+) means a non-active smoking habit; BMI: body mass index.

†Regular use (+) defined as daily intake for a minimum of 6 months.

reduction in the dosage of mycophenolate mofetil and a change to azathioprine and everolimus as soon as clinically possible.

Results

Since 2007, BCG has been used as rescue therapy in five patients who were initially treated with mitomycin C instillations, and as first-line therapy in three additional patients. The clinical and histological findings, including the immunosuppressive therapies of these eight patients, are summarized in Table 2. Seven of these patients are cancer-free after a mean follow-up of 50 months (25–80 months). One patient (N°6) relapsed with CIS after a first cycle of BCG and maintenance therapy followed by a second induction course. She was considered as having failed therapy after 36 months of follow-up and was proposed for radical cystectomy with a trans-ileal cutaneous ureterostomy. Another patient (N°8) relapsed with CIS after a single cycle of BCG for pTa HG and is currently free of any BC after a second induction course of BCG. Representative cystoscopic and histological findings are shown in Figure 1.

The main caveat when using BCG is its associated morbidity, which was expected to be greater in patients taking immunosuppressive agents after transplantation. Actually, the treatment was well tolerated by all patients; one patient (N°5) stopped the therapy after five sessions of the induction cycle because of subjective discomfort, and remains cancer-free after 51 months. There was just one episode of flu-like symptoms during the entire course of the study.

There was no change in the renal graft function, as evidenced by the individual values of serum creatinine before and after BCG instillations (Table 3). In all patients, renal graft function remained satisfactory even years after the last instillation, as reflected by the last biological follow-up (end of 2013 or first semester of 2014).

Discussion

Bladder cancer, the main etiology of which in the general population remains cigarette smoking and occupational exposure to aromatic amines, is estimated to be the 9th most common cause of cancer worldwide and the 13th most common cause of death from cancer. Rates of bladder cancer in men are three times those in women. All patients from this particular population are females, and only two had a past history of smoking habit. More than 90% of newly diagnosed cases of BC are urothelial carcinomas, of which two-thirds are nonmuscle invasive [25]. These tumors can further be subdivided into low, intermediate,

Table 2. Histological findings and therapeutic strategies in kidney transplant recipients diagnosed with non-muscle-invasive bladder cancer 8–20 years after aristolochic acid (AA) exposure.

Patient number	1	2	3	4	5	6	7	8
Age at diagnosis of 1st bladder cancer	59 years	71 years	55 years	67 years	54 years	60 years	72 years	60 years
Immunosuppression	AZA + MPDS	CsA + MMF	CsA + MPDS	CsA + MPDS	CsA + MPDS	TRL + AZA	TRL + MMF	CsA + AZA + MPDS
Time period from start AA to 1st abnormal bladder biopsy	100 months	120 months	96 months	154 months	127 months	242 months	121 months	104 months
Histology	pTa + CIS	PTa HG	CIS	pT_1 LG	pTa + CIS	CIS	pT_1HG	PTa HG
Treatment	TURBT	TURBT	TURBT	TURBT	TURBT	TURBT	TURBT	TURBT
Adjuvant therapy	Mitomycin C	Mitomycin C	Mitomycin C Gemcitabine	Mitomycin C	Mitomycin C	BCG	BCG	BCG
Age at bladder cancer relapse	59 years	73 years	61 years	72 years	57 years	61 years	—	61 years
Immunosuppression	SRL + MPDS	ERL + MPDS	SRL + MPDS	TRL + AZA	SRL + MPDS	TRL + AZA	—	ERL + AZA + MPDS
Histology	CIS	pT_1HG	CIS	pT_1HG	pTa + CIS	CIS	—	CIS
Treatment	TURBT	TURBT	TURBT	TURBT	TURBT	TURBT	—	TURBT
Adjuvant therapy	BCG	BCG	BCG	BCG	BCG	BCG	—	BCG
Follow-up (months)	80	47	25	61	61	36	43	38
Recurrence	None	None	None	None	None	Local*	None	None

BCG, bacillus Calmette-Guerin; CsA, cyclosporin A; TRL, tacrolimus; MMF, mycophenolate mofetil; MPDS, methylprednisolone; SRL, sirolimus; ERL, everolimus; CIS, carcinoma *in situ*; TURBT, transurethral resection of bladder tumor; LG, low-grade; HG, high-grade.
*Multifocal lesions of CIS found in the specimen of cystectomy.

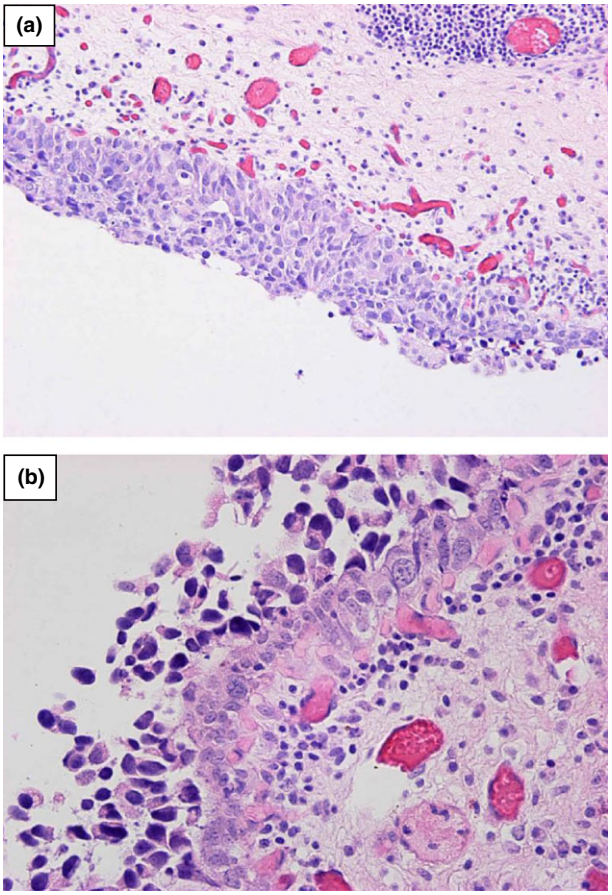

Figure 1 Histological examination of areas detected during a cystoscopy examination in a kidney recipient with end-stage AAN confirming the diagnosis of carcinoma in situ. Photomicrographs at magnification 200× (A) and 400× (B), respectively.

or high-risk groups based on their relative risk of progression. Aristolochic acid exposure is now recognized as a potent risk factor for the subsequent development of urothelial cancer [10]. Because of the high risk of urothelial malignancy related to AA exposure, the prophylactic removal of native kidneys and ureters has been systematically suggested to patients with end-stage AAN in our department [11]. Furthermore, during a prospective 15-year follow-up of screening cystoscopies, a high cumulative incidence of upper tract urothelial carcinoma (39.5%) was identified as a potent risk factor for the subsequent development of BC after kidney transplantation for AAN [17,18]. The average time between the bilateral nephro-ureterectomy and the first BC was 8 years. However, two of our patients were free of neoplasia at the time of surgery (patients N°6 and 7 in Table 1), which confirms the late onset of cancer complications in some cases and the need for further BC screening.

Although the development of BC following renal transplantation is quite rare, transplant recipients are, nevertheless, at an estimated twofold to threefold increased risk of BC because of the immunosuppressive regimen [26]. For that reason, most of our patients were switched from a calcineurin inhibitor to a protocol immunosuppression with mTOR inhibitor, reported to be associated with a reduced incidence of *de novo* malignancies [22–24]. Keeping in mind the high risk of urothelial cancer (incidence and recurrence) in AAN transplanted patients, we suggest that mTOR inhibitors should be considered as first-line therapy in AAN transplant recipients. Especially for patients diagnosed with urothelial cancer (upper urinary tract or bladder), we recommend the switch to mTOR inhibitors.

Table 3. Individual serum creatinine levels before and after bacillus Calmette-Guerin (BCG) (OncoTICE®) instillations, and at the last follow-up (mg/dl). The total amount of instillations per course is provided and the corresponding time periods are indicated between square brackets.

Patient number	1	2	3	4	5	6	7	8
Before BCG	1.2	1.1	1	1.1	1.2	0.7	1.2	1.1
	1.3	1	1.1	1.1		0.6	1.4	1.2
	1.2	0.9	1.1			0.8	1.4	1
		1					1.2	0.9
		1						0.9
Amount of weekly OncoTICE® instillations [year]	6 [2007]	6 [2010]	6 [2011]	6 [2009]	5 [2008]	6 [2010]	6 [2010]	6 [2011]
	2 [2008]	3 [2010]	3 [2012]	7 [2009]		3 [2011]	3 [2011]	3 [2011]
	1 [2009]	3 [2011]	3 [2012]			6 [2011]	3 [2012]	6 [2012]
		3 [2012]					3 [2012]	3 [2012]
		3 [2012]						3 [2012]
After BCG	1.1	1	1.2	1	1.1	0.7	1.1	1
	1.2	1	1	0.9		0.7	1.2	1
	1.3	0.9	1			0.7	1.3	0.9
		0.8					1.2	0.9
		0.9						0.8
At last follow-up [year]	1.5 [2014]	0.9 [2013]	1.2 [2014]	1.1 [2014]	1.4 [2013]	0.8 [2013]	1.2 [2013]	0.9 [2014]

Patients with high-grade NMIBC or CIS can benefit from conservative treatment with BCG. Patients with recurrence or primary muscle-invasive bladder tumor must be evaluated for radical cystectomy. BCG is the treatment of choice for NMIBC with high risk of progression (high-grade tumors and CIS) [27]. The optimal management of BC among renal transplant recipients is not well defined. Intravesical BCG therapy may be considered to be contra-indicated in immunocompromised patients, but because of published reports of successful implementation, we adapted the same therapeutic option for transplanted AAN patients with superficial BC [19]. The additional administration of prophylactic antituberculous treatment attempted to minimize BCG-induced toxicity. Administration of BCG, a live attenuated vaccine, presents a dilemma in graft recipients receiving immunosuppressants. The antitumor mechanism of action of BCG is mediated by stimulation of a marked inflammatory response, with the potential to provoke rejection of the graft, whereas immunosuppressive agents promote an anti-inflammatory response. As graft rejection takes place via the same Th1 pathway immune reaction, BCG can potentially mediate graft loss by an uncontrolled Th1-mediated reaction. On the other hand, inhibition of the Th1 reaction by immunosuppressive drugs can neutralize the antitumor effects of BCG, which would render this treatment ineffective. The decision to use BCG must, therefore, judiciously weight the benefit of BC control against the potential risk of graft loss or ineffective BCG treatment. However, the local intravesical stimulation of immunity has few systemic consequences, especially in terms of maintenance of kidney graft function. And it is a matter to stress that reduction in immunosuppressive doses to decrease the risk of infection and malignancy during BCG courses had no impact on renal function in our population.

Considering these risks, patients benefited from a multidisciplinary screening program with the objective of detecting NMIBC at a stage when conservative therapy is still an option for tumors with low to high risk of progression. Fluorescence-guided biopsy and resection seem more sensitive than conventional procedures for detecting malignant tumors in patients with positive cytology [28].

To the best of our knowledge, this is the first report of a cohort of patients managed with intravesical BCG therapy for AA-related BC in the context of renal transplantation, and with the lowest failure rates of all the studies in other patient cohorts that have been published to date [29–31]. Adjustment of immunosuppressive drug doses and administration of antituberculous prophylaxis are mandatory to optimize this treatment. Nevertheless, despite this treatment, close follow-up and repeated BCG induction, two patients relapsed. This may suggest that other factors intervene in the recurrence of AA-related BC, such as genetic predisposition toward carcinogenesis, initial AA dose and gender [32].

To conclude, we report an encouraging experience with intravesical BCG therapy in AA-related BC in a kidney transplant setting. The local induction of immunity with intravesical instillations of BCG in a context of systemic immunosuppression was effective and limited to the targeted organ, the bladder. This management strategy can be offered to all renal transplant patients fulfilling the same criteria provided that there is strict adherence to the treatment protocol, namely adjustment of immunosuppressants and antituberculous prophylaxis. A multidisciplinary approach, including transplantation nephrologists, urologists, pathologists, and immunologists, is crucial in the management of this complex disease.

Authorship

TR, NB and JLN: participated in the clinical study design, in data analysis, and wrote the article. AJ and AP: collected and analyzed the data. SR: performed the histopathological examinations. VMA and HHS: performed the molecular toxicological analyses. All authors participated in the performance of the research/study, in data interpretation, and approved the final version of the manuscript.

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References

1. Vanherweghem JL, Depierreux M, Tielemans C, *et al.* Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet* 1993; **341**: 387.
2. Vanhaelen M, Vanhaelen-Fastre R, But P, Vanherweghem JL. Identification of aristolochic acid in Chinese herbs. *Lancet* 1994; **343**: 174.

3. Schmeiser HH, Bieler CA, Wiessler M, van Ypersele de Strihou C, Cosyns JP. Detection of DNA adducts formed by aristolochic acid in renal tissue from patients with Chinese herbs nephropathy. *Cancer Res* 1996; **56**: 2025.
4. Cosyns JP, Dehoux JP, Guiot Y, *et al.* Chronic aristolochic acid toxicity in rabbits: a model of Chinese herbs nephropathy? *Kidney Int* 2001; **59**: 2164.
5. Debelle FD, Nortier JL, De Prez EG, *et al.* Aristolochic acids induce chronic renal failure with interstitial fibrosis in salt-depleted rats. *J Am Soc Nephrol* 2002; **13**: 431.
6. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int* 2008; **74**: 158.
7. Gold LS, Slone TH. Aristolochic acid, an herbal carcinogen, sold on the Web after FDA alert. *N Engl J Med* 2003; **349**: 1576.
8. Lewis CJ, Alpert S. Letter to health Care Professionals on FDA concerned about botanical products, including dietary supplements containing aristolochic acid. Us Food and Drug Administration – Center for Food Safety and Applied Nutrition – Office of Nutritional Products. *Labeling and Dietary Supplements*, May 31, 2000.
9. World Health Organization – International Agency for Research on Cancer: IARC monographs on the evaluation of carcinogenic risks to humans: some traditional herbal medicines, some mycotoxins, naphthalene and styrene. *IARC Press, Lyon, France* 2002; 82: 118.
10. World Health Organization – International Agency for Research on Cancer. *IARC Monogr Eval Carcinog Risks Hum* 2011; **100A**: 1.
11. Nortier JL, Muniz-Martinez MC, Schmeiser HH, *et al.* Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). *N Engl J Med* 2000; **342**: 1686.
12. Nortier JL, Schmeiser HH, Muniz-Martinez MC, *et al.* Invasive urothelial carcinoma after exposure to Chinese herbal medicine containing aristolochic acid may occur without severe renal failure. *Nephrol Dial Transplant* 2003; **18**: 426.
13. Gökmen MR, Cosyns JP, Arlt VM, *et al.* The epidemiology, diagnosis, and management of aristolochic acid nephropathy: a narrative review. *Ann Intern Med* 2013; **158**: 469.
14. Jelakovic B, Karanovic S, Vukovic-Lela I, *et al.* Aristoloactam-DNA adducts are a biomarker of environmental exposure to aristolochic acid. *Kidney Int* 2012; **81**: 559.
15. Chen C-H, Dickman KG, Moriya M, *et al.* Aristolochic acid-associated urothelial cancer in Taiwan. *Proc Natl Acad Sci USA* 2012; **109**: 8241.
16. Schmeiser HH, Nortier JL, Singh R, *et al.* Exceptionally long-term persistence of DNA adducts formed by carcinogenic aristolochic I in renal tissue from patients with aristolochic acid nephropathy. *Int J Cancer* 2014; **135**: 502.
17. Lemy A, Wissing KM, Rorive S, *et al.* Late onset of bladder urothelial carcinoma after kidney transplantation for end-stage aristolochic acid nephropathy: a case series with 15-year follow-up. *Am J Kidney Dis* 2008; **51**: 471.
18. Zlotta A, Roumeguère T, Kuk C, *et al.* Select screening in a specific high risk population of patients suggests a stage migration toward detection of non-muscle invasive bladder cancer. *Eur Urol* 2011; **59**: 1026.
19. Palou J, Angerri O, Segarra J, *et al.* Intravesical bacillus Calmette-Guerin for the treatment of superficial bladder cancer in renal transplant patients. *Transplantation* 2003; **76**: 1514.
20. Eble J, Sauter G, Epstein J, Sesterhenn I. *World Health Organization Classification of Tumours. Pathology & Genetics. Tumours of the Urinary System and Male Genital Organs*. Lyon: IARC Press, 2004: pp. 90–157.
21. Sobin L, Gospodarowicz M, Wittekind C. *International Union against Cancer. TNM Classification of Malignant Tumours*, 7th edn. Oxford, England: Wiley-Blackwell, 2009: pp. 262–265.
22. Campistol JM, Eris J, Oberbauer R, *et al.* Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17**: 581.
23. Schena FP, Pascoe MD, Alberu J, *et al.* Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation* 2009; **87**: 233.
24. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005; **80**: 883.
25. Parkin DM. The global burden of urinary bladder cancer. *Scand J Urol Nephrol* 2008; **218**: 12.
26. Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer incidence among Canadian kidney transplant recipients. *Am J Transplant* 2007; **7**: 941.
27. Babjuk M, Oosterlinck W, Sylvester R, *et al.* EAU guidelines on non-muscle invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol* 2011; **59**: 997.
28. Stenzl A, Penkoff H, Dajc-Sommerer E, *et al.* Detection and clinical outcome of urinary bladder cancer with 5-aminolevulinic acid-induced fluorescence cystoscopy: a multicenter randomized, double-blind, placebo- controlled trial. *Cancer* 2010; **117**: 938.
29. Tillou X, Raynal G, Limani K, Saint F, Petit J. Carcinoma in situ in bladder and urethra among renal transplanted patient: failure of BCG therapy. *Prog Urol* 2008; **18**: 1097.
30. Sun HY, Singh N. Should intravesical Bacillus Calmette-Guérin be employed in transplant recipients with bladder carcinoma? *Transpl Infect Dis* 2010; **12**: 358.
31. Tomaszewski J, Larson J, Smaldone M, Hayn MH, Jackman S. Management of bladder cancer following solid organ transplantation. *Adv Urol* 2011; **2011**: Article ID 256985. doi: 10.1155/2011/256985.
32. Chiong E, Kesavan A, Mahendran R, *et al.* NRAMP1 and hGPX1 gene polymorphism and response to bacillus Calmette-Guérin therapy for bladder cancer. *Eur Urol* 2011; **59**: 430.