European Journal of Cancer Vol. 32A, No. 1, pp. 175–176, 1996.

Printed in Great Britain
0959–8049/96 $15.00 + 0.00

0959-8049(95)00514-5

High Frequency of Urothelial Cancers in Patients with Kidney Transplantations for End-stage Analgesic Nephropathy

C. Bokemeyer,[1] W.F. Thon,[2] T. Brunkhorst,[3] M.A. Kuczyk,[2] R. Pichlmayr[4] and V. Kliem[3]

Departments of [1]Haematology/Oncology, [2]Urology, [3]Nephrology and [4]Abdominal and Transplant Surgery, Hannover University Medical School, Konstanty-Gutschow-Str. 8, 30625 Hannover, Germany

RENAL TRANSPLANTATION is the treatment of choice for patients with end-stage renal disease [1]. In Germany, the prevalence of analgesic nephropathy in dialysis patients is approximately 6% according to the European Dialysis and Transplant Association [2]. Nephropathy following analgesic abuse, particularly phenacetin, was described as early as 1953 [3]. It has also been recognised that analgesic abuse is associated with an increased risk for the development of urothelial cancer, in particular tumours of the renal pelvis and bladder. Urothelial tumours were found in 8–15% of autopsies from a series of patients where excessive use of analgesic drugs was evident, and in many cases multifocal tumours, involving the bladder, ureter or renal pelvis were detected [4].

Irrespective of the risk of urothelial cancers after analgesic abuse, an increased incidence of malignancies following renal transplantation ranging from 4 to 18% at 5–10 years of follow-up has been reported [5]. The highest risk was observed for skin cancers and lymphomas and their occurrence has been attributed to the use of immunosuppressive agents such as cyclosporine after renal transplantation [6]. Only few reports have addressed the frequency and clinical outcome of urothelial cancers in patients undergoing renal transplantation for analgesic nephropathy.

The current retrospective analysis focuses on the frequency and clinical course of urothelial cancers in patients receiving renal transplants for analgesic nephropathy at Hannover University Medical School between 1968 and 1993. In total, 2072 patients underwent 2371 renal transplantations during this time period, including 65 patients (3.1%) transplanted for analgesic nephropathy. All patients were routinely followed after transplantation by abdominal ultrasound and urine cytology at half-yearly intervals and the median follow-up for the total group of patients was 9.1 years (1–25 years).

Urothelial tumours occurred in 11 of 65 patients (16.9%) (95% confidence interval, CI: 7.6–26.2%) transplanted for analgesic nephropathy in comparison to 2 of 2007 patients (0.1%) (95% CI: 0–0.24%) transplanted for other causes of end-stage renal disease ($P < 0.001$). 3 of the 11 patients with urothelial cancer and analgesic abuse had multifocal disease, accounting for a total of 15 cancers of the urinary tract among 65 patients (23.1%). The median age of the patients at the time of diagnosis of urothelial cancer was 56 years (range: 51–66 years) and 9 women and 2 men were affected. The median time since the start of dialysis was 72 months (range: 42–108 months) and the median time since renal transplantation and the start of immunosuppression with cyclosporine was 34 months (range: 4–75 months). Only 4 patients had tumours in the bladder alone and 8 of 15 urothelial tumours were localised outside the bladder (ureter 1, renal pelvis 7). The localisations of the urothelial tumours, tumour stage, grade, therapy and follow-up of the 11 patients are summarised in Table 1. 8 of the 15 tumours (53%) were already ≥T2-stages at diagnosis and 3 patients already had metastatic disease (lymph nodes 2 patients; bone metastases 1 patient). After the median follow-up of 6 years, 8 patients had died: 6 patients due to recurrent urothelial cancer [median survival 17 months since diagnosis (range: 4–33 months)], 1 patient from postoperative complications following cystectomy and 1 patient from non-tumour related causes.

Our analysis of 2072 kidney transplanted patients demonstrates a cumulative incidence of 16.9% of patients developing urothelial cancers after prior analgesic abuse in contrast to a general frequency of 0.1% of urothelial cancers in those patients transplanted for other causes of end-stage renal disease. This demonstrates that the development of urothelial cancers in renal transplant patients is largely confined to the high risk group with end-stage renal failure due to analgesic nephropathy. Although it cannot be excluded that the use of immunosuppresive therapy may accelerate rapid growth—as may be concluded from the short median survival time of 17 months in these patients—immunosuppression does not seem to increase the incidence of urothelial tumours in non-analgesic abused patients receiving renal transplants. The relative risk for death from urothelial cancer in patients with analgesic abuse has been reported as between 2.3 for bladder cancer up to 12.2 for urothelial cancer of the renal pelvis [4, 7, 8]. Routine follow-up investigations, such as exfoliative urinary cytology and abdominal ultrasound, in transplant patients at risk of urothelial cancer have a low sensitivity in detecting urothelial neoplasms localised in the ureter and the renal pelvis. Urine cytology is not very helpful because the voided urine results from the transplanted kidney and does not pass through the upper urinary tract. Retrograde ureteropyelography with a fractioned lavage cytology is a more effective diagnostic procedure in this subgroup of patients [9]. Other series have reported urothelial cancer of the upper urinary tract in 4.7–9.1% of renal transplant patients with analgesic nephropathy [10]. Furthermore, in 27 of 56 patients undergoing prophylactic nephro-ureterectomy before or shortly after kidney transplantation for analgesic nephropathy, urothelial dysplasias were histologically found. One third of patients had tumours at multiple localisations in the urinary tract [7].

Correspondence to C. Bokemeyer.
Revised 14 Aug. 1995; accepted 18 Sep. 1995.

Table 1. Tumour localisations, symptoms, presenting therapy and outcome of 11 patients developing urothelial cancers after renal transplantation for end-stage analgesic nephropathy

Symptoms/findings at diagnosis (patients)		Localisation of urothelial cancer (patients)		Tumour stages at diagnosis* (patients)		Therapy (patients)		Outcome (patients)	
Haematuria	(5)	Bladder	(4)	pTa/pT1	(3)	Nephro-ureterectomy	(6)	DOD	(7)
Positive cytology	(4)	Renal pelvis	(4)	pT2	(5)	Transurethral resection	(3)	TRD	(1)
Positve ultrasound	(2)	Renal pelvis + bladder	(2)	pT3	(3)	Cystectomy	(2)	DEAD	(1)
Bone metastases	(1)	Renal pelvis + bladder + ureter	(1)					NED	(2)

DOD, dead of disease; TRD, therapy-related death; DEAD, death from non-tumour-related causes; NED, no evidence of disease; * Highest T-category per patient given in cases of multifocal disease.

The clinical outcome of therapy for urothelial cancer in patients with renal transplants is poor and from our 11 patients, 7 died from recurrent tumour after surgery, 1 from surgical-related complications and 1 from other causes. The median survival of 17 months is very short and may in part be explained by the fact that many tumours were detected at advanced stages due to their localisation in the upper urinary tract. Based on the high incidence, the predominant localisation in the upper urinary tract and the poor outcome of urothelial cancers after renal transplantation in patients with analgesic nephropathy, prophylactic bilateral nephro-ureterectomy should be prospectively evaluated after successful renal transplantation in this high risk group of patients. Currently, the prophylactic radical surgical removal of the possibly altered urothelium of the upper urinary tract and close follow-up of the urothelium of the bladder by routine cystoscopies might be the only approach that will have substantial impact on the long-term survival of patients with analgesic nephropathy who have received successful renal transplants.

1. Suthantiran M, Strom TB. Renal transplantation. *N Engl J Med* 1994, **331**, 365–376.
2. Wing AJ, Broyer M, Brunner FP, *et al.* Combined report on regular dialysis and transplantation in Europe, XIII, 1982. *Proc EDTA* 1983, **20**, 5.
3. Spühler O, Zollinger HU. Die chronische interstitielle Nephritis. *Z Klin Med* 1953, **151**, 1–50.
4. Bengtsson U, Angervall L, Ekman H, Lehmann L. Transitional cell tumours of the renal pelvis in analgesic abusers. *Scand J Urol Nephrol* 1968, **2**, 145–150.
5. Frei W, Bode U, Repp H, *et al.* Malignancies under cyclosporine after kidney transplantation: analysis of a ten year period. *Transplant Proc* 1993, **25**, 1394–1396.
6. Pecqueux JC, Schwarz A, Dieckmann KP, Offermann G. Cancer incidence in patients on chronic dialysis and in renal transplant recipients. *Urol Int* 1990, **45**, 290–292.
7. Charbit L, Gendreau MC, Mee S, Cukier J. Tumors of the upper urinary tract: 10 years of experience. *J Urol* 1991, **146**, 1243–1246.
8. Huben RP, Mounzer AM, Murphy GP. Tumor grade and stage as prognostic variables in uppertract urothelial tumors. *Cancer* 1988, **62**, 2016–2020.
9. Hruby von W, Stellamor K, Zinner G, Marberger M. Der Nierenbeckentumor im Sonogramm. *Fortschr Roentgenstr* 1983, **138**, 469–472.
10. Blohme I, Johansson S. Renal pelvic neoplasms and atypical urothelium in patients with end-stage analgesic nephropathy. *Kidney Int* 1981, **20**, 671–675.

European Journal of Cancer Vol. 32A, No. 1, pp. 176–177, 1996.

Printed in Great Britain
0959–8049/96 $15.00 + 0.00

0959-8049(95)00466-1

Lonidamine plus Epirubicin and Cyclophosphamide in Advanced Breast Cancer. A Phase II Study

G. Gardin,[1] C. Barone,[2] O. Nascimben,[3] G. Ianniello,[4] F. Sturba,[5] A. Contu,[6] P. Pronzato[7] and R. Rosso[1]

[1]Divisione di Oncologia Medica I, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, n.10, 16132 Genova; [2]Università Cattolica del S. Cuore, Policlinico A. Gemelli, Roma; [3]Ospedale Civile Umberto I, Mestre; [4]Ospedale Civile, Benevento; [5]Ospedale Generale Regionale, Ancona; [6]Ospedale Civile, Sassari; [7]Servizio di Oncologia Medica, Ospedale Civile S. Andrea, La Spezia, Italy

LONIDAMINE, a dichlorinated derivative of indazole-3-carboxylic acid, belongs to a new class of anticancer agents with a unique mechanism of action. Initial *in vitro* studies suggested that lonidamine could affect the energy metabolism of cancer cells by inhibiting oxygen consumption and aerobic glycolysis [1]. Mitochondria have been found to be the primary intracellular target of this drug [2]. Clinical evaluation of lonidamine in different types of malignancies has been conducted in American and European institutions [3–7]. In our previous experience, we

Correspondence to G. Gardin.
Revised 2 Aug. 1995; accepted 10 Aug. 1995.