—Report on Experiments and Clinical Cases—

Transitional Cell Carcinoma of the Bladder in Four Patients on Maintenance Hemodialysis

Kazutaka Horiuchi, Takushi Uchikoba, Fumiatsu Oka, Mitsuhiro Sato, Yukihiro Kondo, Go Kimura, Narumi Tsuboi, Kazuhiro Yoshida and Taiji Nishimura

Department of Urology, Nippon Medical School

Abstract

We report four patients on maintenance hemodialysis (HD) with transitional cell carcinoma (TCC) of the bladder. Three patients underwent transurethral resection (TUR) of their tumors, which were grade 2 or 3, stage pT1 TCC. Among them, one patient underwent repeat TUR for recurrent superficial TCC. The remaining one patient underwent total cystectomy for grade 3, stage pT4 TCC and squamous cell carcinoma of the bladder. Subsequently, he died suddenly without evidence of local recurrence or systemic metastasis. We discuss the relationship between the duration of HD and the tumor grade and stage of primary bladder TCC in maintenance HD patients.
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Key words: transitional cell carcinoma, bladder, hemodialysis

Introduction

As a result of efforts to develop more effective and safer maintenance hemodialysis (HD) techniques, patients with chronic renal failure now survive longer than before. However, this prolongation of survival has increased the risk of HD patients developing malignant tumors. The incidence of bladder tumors is higher in HD patients than in the general population of Japan[1] or other countries[2,3].

Ryoji et al. have reported their clinical findings of bladder tumors, including secondary bladder TCC and adenocarcinoma or squamous cell carcinoma of the bladder, in hemodialysis patients in Japan[4]. However, there have been no published reports evaluating primary bladder TCC in maintenance HD patients. Therefore, we herein report our experience with four patients on maintenance HD who developed bladder TCC, and discuss clinical findings of primary bladder TCC, and especially the relationship between the duration of HD and the tumor grade and stage based on case reports published in Japan[4–7].

Case Reports

Case 1

An 81-year-old man on maintenance HD for 13 years presented with gross hematuria. He underwent transurethral resection (TUR) of multiple papillary bladder tumors, which were pathologically found to be grade 3, stage pT1b TCC. He then received intravesical mitomycin C (MMC: 20 mg dissolved in 20 m*l* of distilled water), once a week for 10 weeks with no adverse effects. He was

Correspondence to Kazutaka Horiuchi, Department of Urology, Nippon Medical School Second Hospital, 1–396 Kosugi-cho, Nakahara-ku, Kawasaki-shi, Kanagawa 211–8533, Japan
E-mail: kazu0809@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

susequently followed for 27 months without evidence of recurrence. This was a case worthy of note, because he had the longest duration of dialysis before tumor recovery among all the maintenance HD patients with superficial bladder TCC reported in Japan.

Case 2

A 69-year-old man on maintenance HD for 14 months presented with gross hematuria. He underwent TUR, followed by total cystectomy, for multiple papillary and non-papillary bladder tumors. These tumors were pathologically grade 3, stage pT4 bladder TCC partially including squamous cell carcinoma associated with pelvic lymph node metastases. He died suddenly at four months after surgery without evidence of local recurrence or systemic metastasis. The cause of death was unknown because no autopsy could be performed.

Case 3

A 57-year-old man on maintenance HD for 10 months presented with gross hematuria. He underwent TUR for a solitary papillary bladder tumor, which was pathologically found to be grade 2, stage pT1 TCC. After TUR, we administered MMC at the same dose as that used to treat Case 1 for 6 weeks with no adverse effects. He was then followed for 11 months without evidence of recurrence.

Case 4

A 66-year-old woman on maintenance HD for 10 months presented with gross hematuria. She underwent TUR for multiple papillary bladder tumors that were pathologically grade 3, stage pT1 TCC. After surgery, we administered MMC at the same dose as that used to treat Case 1 for 6 weeks with no adverse effects. Three months after the first operation, she underwent repeat TUR for a solitary recurrent bladder tumor, which was pathologically found to be grade 3, stage pT1 TCC associated with carcinoma in situ. After the second TUR, we gave intravesical pirarubicin hydrochloride (20 mg dissolved in 20 m*l* of distilled water) once a week for 6 weeks with no adverse effects. She was followed for 12 months after the second TUR procedure without evidence of recurrence.

The characteristics of the four above patients are summarized in **Table 1**.

Discussion

Table 2 shows the relationship between the duration of HD and tumor grade or stage in 47 maintenance HD patients with primary bladder TCC that were previously reported in the Japanese literature[4–7] plus our four patients.

Concerning tumor grade, all of our four patients had grade 2 or 3 tumors, and the overall prevalence of high-grade tumors (grade 2 or 3) was 86%, with grade 3 tumors accounting for 63%. The incidence of high-grade tumors was higher than in the general population irrespective of the duration of HD, so the duration of chronic renal failure seems to play a more important role than the duration of HD in the occurrence of high-grade bladder TCC.

Regarding tumor stage, a strong correlation exists between tumor grade and tumor stage in the general population. However, the incidence of superficial tumors during the first year of HD was similar to that in the general population in spite of the high incidence of high-grade tumors. The incidence of invasive tumors after the second year of HD was higher than that in the general population, and it kept on increasing to account for two thirds of all tumors after the third year of dialysis. Therefore, the duration of HD also may play an important role in the occurrence of high-stage bladder TCC.

An increased incidence of bladder tumors is observed in patients with end-stage renal disease (ESRD) or on maintenance HD[1–3]. A multitude of factors associated with renal disease and the maintenance HD treatment itself may contribute to increased tumor formation in the bladder in these patients[8]. Impaired function of the immune system[9] and DNA repair mechanisms[10,11] are found more frequency in patients with ESRD or on maintenance HD. However, the reasons why patients on maintenance HD have an increased risk of high-grade bladder TCC are still uncertain. There are strong molecular and cytogenetic data to support the well-established clinical impression that low-

Table 1 Characteristics of our four patients

	Case 1	Case 2	Case 3	Case 4
Age (years)	81	69	57	66
Sex	male	male	male	female
Primary renal disease	CGN	CGN	DN	uncertain
Period of hemodialysis	13Y	1Y2M	10M	10M
Urine volume/day	100 m*l*	500 m*l*	700 m*l*	500 m*l*
Chief complaint	GH	GH	GH	GH
Histology				
cell type	TCC	TCC > SCC	TCC	TCC
grade (G)	3	3	2	3
stage (pT)	1	4	1	1
papillary (P)/non-papillary (NP)	P	P + NP	P	P
single (S)/multiple (M)	M	M	S	M
infiltration pattern (INF)	α	γ	β	α
lymph duct invasion (ly)	0	1	0	0
venous invasion (v)	0	1	0	0
carcinoma in situ	−	−	−	+
Operation	TUR-Bt	Total Cx	TUR-Bt	TUR-Bt
Prophylactic treatment	MMC 20 mg/ w × 10 w	—	MMC 20 mg/ w × 10 w	THP 30 mg/ w × 6 w
Prognosis				
alive (A)/dead (D)	A, 21M	D, 4M	A, 11M	A, 12M
recurrence (R)/metastasis (M)	R − /M −	R − /M −	R − /M −	R + /M −

Abbreviations:
CGN = chronic glomerulonephritis DN = diabetes nephropathy GH = gross hematuria TCC = transitional celll carcinoma SCC = squamous cell carcinoma TUR-Bt = transurethral resection of the bladder tumor Total Cx = total cystectomy MMC = mitomycin c THP = pirarubicin hydrochloride

Table 2 Relationship between duration of hemodialysis and tumor grade or stage

Duration of hemodialysis	During 1st year (n = 14)	During 2nd year (n = 10)	During 3rd year (n = 9)	After 3rd year (n = 18)	Total (n = 51)
Grade (G)					
G 1	1 (7%)	4 (40%)	1 (11%)	1 (6%)	7 (14%)
G 2	4 (29%)	2 (20%)	2 (22%)	4 (22%)	12 (24%)
G 3	9 (64%)	4 (40%)	6 (67%)	13 (75%)	32 (63%)
G 2 + G 3	13 (93%)	6 (60%)	8 (89%)	17 (94%)	44 (86%)
Stage (pT)					
pTa + pT1	10 (71%)	5 (50%)	3 (33%)	6 (33%)	24 (47%)
pT2 <	4 (29%)	5 (50%)	6 (67%)	12 (67%)	27 (53%)

grade and high-grade bladder TCC have fundamentally different origins, with the former losing one or more suppressor genes on chromosome 9 and the latter having p53 abnormalities as early initiating events in the general population[12]. So bladder TCC in patients with ESRD or on maintenance HD may also tend to acquire p53 mutations as early initiating events for some reason.

Early diagnosis is important, because many patients on maintenance HD have high-grade and high-stage disease when their bladder TCC is found. For early diagnosis, periodic urine cytology should be performed and cytology of bladder washings is useful for patients whose urine output is small. Furthermore, it is very important to immediately perform cystoscopy at the onset of macroscopic hematuria in order to detect bladder TCC as early as possible.

Intravesical prophylaxis with bacille Calmette-Guérin (BCG) is generally accepted as being effective for postponing or preventing recurrence and/or progression of high-grade superficial bladder TCC in the general population[13]. Although Yoshihiro et al.[14] reported that BCG was also effective and safe for HD patients, we hesitated to use this therapy because HD patients are immunodeficient relative to the general population. Further research is needed to determine whether BCG prophylaxis is actually safe and effective for HD patients with superficial TCC of the bladder.

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