

CONCEPTS IN THE TREATMENT OF BLADDER CANCER—CLINICAL AND EXPERIMENTAL

Mark S. SOLOWAY, M. D.

Professor, Department of Urology, University of Tennessee Center for the Health Sciences

Assessment of optimal management of a patient with bladder cancer will be dependent on tumor grade, stage and multiplicity as well as the patient's medical status. Thus the urologist should attempt to assess the extent of urothelial abnormality and obtain as accurate a stage as possible. Despite endoscopy, biopsy, and bimanual examination under anesthesia, the precise depth of invasion is often inaccurate when dealing with a tumor which has invaded into the muscle. Newer techniques such as endoscopic ultrasound and CAT scan may allow the clinician to improve his accuracy in gauging the stage of invasive tumors. Selected site cold cup biopsies are advantageous in determining the extent of urothelial abnormalities, e.g. dysplasia, carcinoma *in situ* (CIS). Prognosis is largely dependent on the depth of tumor invasion, with the likelihood of dissemination much greater once the tumor has invaded into the muscular wall of the bladder. Thus those patients with stage Ta, T1 or Tis are managed endoscopically with supplemental intravesical chemotherapy and those with T2 or greater lesions are treated with radiation and/or extirpative surgery.

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SUPERFICIAL BLADDER CANCER

Endoscopy

The urologist can gain a great deal of information at the time of the initial endoscopic evaluation. It is critical to closely evaluate all portions of the bladder and often this will require complete bladder relaxation utilizing either a general or regional anesthesia. A bladder diagram should be available so the endoscopist can make a permanent record of the number and size of each identifiable urothelial abnormality and the site of the biopsies. At this initial evaluation the selected site biopsies can be quite helpful in determining the extent of urothelial abnormalities. Usually these selected site biopsies are obtained lateral to each ureteral orifice, the posterior midline, and the dome. A biopsy from the prostatic urethra might be warranted in men with multifocal disease, tumor located near the bladder neck, or carcinoma *in situ*.

Any visible tumor should be resected as completely as possible with the surrounding urothelium fulgurated. The completeness

of resection obviously depends upon the extent of disease.

Pathology

The majority of urothelial tumors appears as exophytic neoplasms in which the cells are arranged on fibrovascular stalks. These papillary tumors are usually of low cytologic grade; however they have a marked propensity for "recurrence". There may be a mixture of cytologic grades (I–III) within each neoplasm.

Tumors which are flat or sessile are thought to develop from urothelial atypia or dysplasia without concomitant hyperplasia. Because there is no fibrovascular stalk; it may be difficult to identify these lesions endoscopically. There is a paucity of information on the natural history of these flat lesions. The terms "dysplasia" or "atypia" correspond by nature of their cellular architecture to grade I or grade II papillary tumors. Therefore it might be logical to term these lesions flat, transitional cell carcinoma grade I and II. It is probably preferable, however, to retain the term "dysplasia" until the exact relationship

of these lesions to carcinoma is better understood. On the other hand, flat tumors of high cytologic grade (III) are termed appropriately "carcinoma *in situ*".

Carcinoma *in situ* is often multifocal and the cells lack an orderly progression from the basal layer to the surface. Nuclear pleomorphism is prominent. Mitoses may be frequent. Carcinoma *in situ* is not always endoscopically apparent and selected site or random mucosal biopsies of endoscopically normal-appearing urothelium will frequently identify CIS. It should be emphasized that the natural history of carcinoma *in situ* is quite variable.

Cytology

Cytologic evaluation of urine obtained by voiding, via the cystoscope, or by bladder washing has become an integral part of the total evaluation of patients with urothelial carcinoma. Since the accuracy of urinary cytology is high with lesions of higher cytologic grade, it is particularly helpful in the detection of carcinoma *in situ*. A positive cytology in a patient with a grade I tumor might alert the urologist to be suspicious of a higher grade neoplasm since grade I tumors differ only slightly in their cytologic features from those of normal urothelial cells and thus they are not usually identifiable on examination of the urine. With increasing reliance on cytology as a sampling of the urothelium, the frequency of endoscopy might be reduced in patients being monitored following resection of a superficial tumor if the cytopathologist is experienced and the cytology is negative.

Although intravesical chemotherapy can produce some cytologic alterations in exfoliated urothelial cells, the experienced cytopathologist can usually distinguish these effects from malignant cells. It is critical, however, that the clinician provide the cytopathologist with pertinent data related to the patient's prior therapy, e.g. intravesical chemotherapy, systemic chemotherapy, radiation.

New Occurrences vs. True Recurrences

The five-year survival for patients with superficial bladder cancer is excellent,

ranging from 63–82 per cent. The chance, however, of a subsequent tumor is quite high, ranging from 50–70 per cent¹⁻⁴⁾. There are probably two separate etiologies for this high incidence of subsequent tumors. Histologic mapping of the bladder following cystectomy for invasive bladder cancer has demonstrated multifocal carcinoma or carcinoma *in situ* in approximately 80 per cent of specimens⁵⁻⁷⁾. Further evidence for multifocal neoplasia comes from studies in which mucosal biopsies have been obtained from normal-appearing mucosa at sites distant from an obvious tumor. The incidence of urothelial dysplasia, CIS, or cancer in these specimens ranges from 20–80 per cent⁸⁻¹⁰⁾.

The second possible explanation for the high incidence of subsequent tumors following endoscopic resection/fulguration may be the implantation of tumor cells following the operative procedure. These should be termed true recurrences. Trauma to the urothelium during the endoscopic procedure may provide a fertile site for viable tumor cells to implant and grow.

Although implantation has been conjectured as a possible reason for the high incidence of subsequent tumors, there has been little experimental data until recently to confirm this hypothesis. MacDonald and Thorson¹¹⁾ successfully transplanted transitional cell tumors to mucosal-lined pouches previously created in recipient dogs. Weldon and Soloway¹²⁾ showed a 60 per cent incidence of transitional cell tumor implantation in mice following pre-treatment of the bladder with n-methyl-n-nitrosourea (MNU). There was only a 13 per cent incidence of implantation in bladders without prior alteration. MNU produces a diffuse cystitis and epithelial denudation presumably allowing sites for tumor implantation. MNU treatment, however, may not simulate the clinical situation. Thus a technique was devised to reproducibly cauterize a small portion of the murine urothelium¹³⁾. These two methods were recently compared.

The animals used were female C3H/He mice. The tumor, MBT-683, is a poorly differentiated transitional cell carcinoma

which originated as an invasive neoplasm in a female C3H/He mouse which had ingested the carcinogen FANFT for eleven months. The tumor has been serially transplanted in syngeneic mice and was utilized in its thirtieth transplant generation. A single cell suspension of this tumor was prepared by trypsin enzymatic dissociation as previously described¹⁴.

Fifty-seven C3H/He mice were randomly divided into three groups. Group I (16 mice) served as controls and received the tumor cell suspension intravesically. Group II (25 mice) had urothelial injury produced by intravesical MNU prior to instillation of the tumor cell suspension. Group III (16 mice) had urothelial damage produced by cauterization prior to insertion of tumor cells.

The mice receiving the MNU received a fresh solution of 7.5 mg/cc. A total of 0.1 cc was injected intravesically. This was performed two days prior to instillation of the tumor cells. The drug was placed into the bladder via a small urethral polyethylene catheter.

Mice in Group III had the posterior portion of the bladder cauterized by a transurethrally placed insulated electrode which was attached to a Bovie electrocautery unit. Perforation of the bladder occurred in three animals and an additional mouse died four days following cauterization presumably of infection. Thus 12 mice were analyzed for tumor development.

All mice received 2.09×10^6 viable MBT-683 transitional tumor cells in a volume of 0.1 cc. The cells were instilled transurethrally. Mice were observed for 28 days. Bladders were removed and evaluated for the presence of tumor.

Tumors developed in one of 16 (6%) mice in the control group (Group I) (Table

1). The incidence of tumor was 28 per cent (7 of 25) in the mice pre-treated with MNU two days prior to the intravesical instillation of tumor cells. This difference was not statistically significant, $p < 0.1$.

Mice in Group III which had the posterior portion of the bladder fulgurated immediately prior to instillation of tumor cells exhibited 67 per cent incidence of bladder tumors. This difference is highly significant, $p < 0.005$, and confirms that transitional tumor cells will preferentially implant on the altered urothelial surface.

There is increasing evidence which suggests that some of the subsequent tumors seen following endoscopic resection in man may be true recurrences resulting from implantation. Urologists have often commented on the frequency of subsequent tumors at the vesical neck, in the prostatic urethra, or in the bladder dome and have implicated trauma from the initial resection^{15,16}. This circumstantial evidence as well as the different sites of "recurrent" tumors when compared to initial tumors was the subject of a recent review article¹⁷.

Intravesical Chemotherapy

Since both multifocal new tumor occurrence and implantation appear to contribute to the high incidence of subsequent tumors, it seems futile to rely solely on transurethral resection for the long-term management of patients with superficial bladder cancer. This is particularly true for those that have demonstrated a likelihood for frequent recurrences. Topical chemotherapy initiated shortly after surgical resection might reduce the likelihood of true recurrences by eradicating viable tumor cells remaining in contact with the urothelium after endoscopic surgery and might also diminish the number or frequency of new occurrences by exerting a cytotoxic action on the microscopic foci of carcinoma or CIS. Intravesical instillation of chemotherapeutic agents places a relatively high concentration of drug in contact with the urothelium while minimizing systemic toxicity. The agent most frequently utilized for intravesical chemotherapy is thio-tepa. This agent has been carefully evaluated both as definitive

Table 1. Comparison of MNU and cauterization on the incidence of tumor cell implantation

		NO. MICE	WITH TUMOR	%	P*
I	NORMAL MUCOSA	16	1	6	
II	MNU PRETREATMENT	25	7	28	N.S.
III	CAUTERIZATION	17	8	67	<0.005

* CHI SQUARE

Table 2. Definitive therapy of superficial bladder tumors with thio-tepa

AUTHORS	No. PTS.	COMPLETE (%)	PARTIAL (%)	NONE (%)
VEENEMA ET.AL. ¹⁸	46	37	35	28
ABBASSIAN AND WALLACE ¹⁹	13	23	38	38
EDSYMR AND BOWMAN ²⁰	19	41	41	17
KOONTZ ET.AL. (NBCCGA) ²¹	95	47		58

therapy of existing superficial tumors as well as for prophylaxis following complete endoscopic resection/fulguration.

The reported response rate, including both complete and partial responses when utilized for definitive therapy of patients with multiple papillary tumors, ranges from 47–82 per cent^{18–21} (Table 2). The dose usually employed consists of four weekly instillations of 30–60 mg diluted in an equal volume of sterile water followed by a monthly dose. The major side effect of this drug is myelosuppression.

There is a lack of long-term follow-up on patients receiving thio-tepa for definitive therapy of superficial bladder cancer. Thus although there is a high likelihood that the drug is of initial benefit, the subsequent incidence of tumors while receiving maintenance thio-tepa has not been determined.

In an effort to better define the histologic and cytologic alterations resulting from repeated thio-tepa instillations, we have carried out a series of experiments utilizing an animal model to avoid the uncontrolled variability inherent in human studies and permit the examination of the entire bladder following thio-tepa instillation for comparison with histologic and cytologic findings. The initial investigation²² analyzed the effect of a single dose of thio-tepa (compared to saline) on the normal murine urothelium. No consistent morphologic differences were encountered between the two solutions. In particular there were no atypical cells such as described in association with irradiation or cyclophosphamide.

A subsequent series of studies^{23–24} evaluated the effect of thio-tepa on the induction of urothelial tumors by the carcinogen FANFT. Thio-tepa or saline was initiated when the animals were known to have

either atypia or carcinoma *in situ*. Following three weeks of therapy, prominent cellular degeneration and vacuolization were observed both by urine cytology and histology and are believed to represent toxic effects of therapy. These effects were not limited to the drug-treated group but were also seen in animals receiving saline. They were, however, more prominent in those treated with the alkylating agent. Nuclear changes which might reflect alterations of cellular metabolism were uncommon. The incidence of tumors did not significantly differ between the treated and control animals. There were, however, significantly fewer high stage tumors in the thio-tepa treated group compared to the controls. This suggests that thio-tepa retarded the progression of neoplasms from low grade, non-invasive lesions to high grade, invasive lesions.

If these animal studies reflect what occurs in the human, thio-tepa may cause denudation of papillary growth with resultant flattening of fibrovascular stalks rendering them endoscopically invisible. Thus the effect of therapy as denoted by endoscopy, will be recorded as a complete response although abnormal basal cells may not be eradicated. Thus given sufficient time, the tumor would reappear. This, of course, does not negate the beneficial effects of thio-tepa since such a denuding action might spare the patient repeated endoscopic sessions for fulguration of low grade tumors. In addition, the toxic effect of the drug may prevent implantation of tumor cells when instilled following a transurethral resection.

A number of studies^{21,25–27} have now compared the efficacy of thio-tepa prophylaxis compared to a non-treated group.

Table 3. Incidence of recurrence following thio-tepa prophylaxis

AUTHORS	NO. PTS.	CONTROL (%)	THIO-TEPA (%)
BURNAND ET. AL. ²⁵	51	97	58
BYAR AND BLACKARD (VA) ²⁶	88	60	47
SCHULMAN ET. AL. (EORTC) ²⁷	224	52	49
KOONTZ ET. AL. (NBCCGA) ²¹	93	66	40

(Table 3) The dosage, administration schedule, and, in particular, the delay in the initiation of the drug following resection of tumors vary widely in the studies. Burnand et al.²⁵ found minimal side effects following instillation of a single 90 mg dose immediately post-resection. The drug remained in the bladder for only 30 minutes. England et al.²⁸ utilized thio-tepa in 40 patients as prophylaxis following endoscopic resection of multiple tumors. Twenty-seven of the patients had grade I and 13 had grade II lesions. All of the patients with grade II tumors had invasion into the lamina propria. The 30 mg dose was instilled on days 1, 3, and 5 post-surgery. The authors considered patients as responding if there was no recurrence or if the incidence of subsequent tumors was reduced to a small fraction of the established previous pattern. Thirty-one (78 per cent) of the treated patients responded. There was no difference in the response rate between patients with grade I or grade II tumors. Of 13 patients with grade II, stage T1 lesions, only two failed to respond. Twenty-six per cent of the responders have remained tumor-free without thio-tepa maintenance. Three of the entire group of patients died of bladder cancer during the follow-up. The responders could usually be denoted after the first course of intravesical therapy. Usually there was a reduction in the number of subsequent tumors with eventual clearance confirmed by selected site mucosal biopsies.

There have been two recent multi-institutional collaborative group studies evaluating the prophylactic effect of thio-tepa following endoscopic resection/fulguration of superficial bladder cancer. The National Bladder Cancer Clinical Collaborative

Group²¹ compared prophylactic thio-tepa utilizing either 30 or 60 mg compared to a group not receiving chemotherapy. Therapy was initiated one month following resection. The disease-free incidence at one year was 66 per cent for those who received thio-tepa compared to 40 per cent in the control group. This was a statistically significant difference, $p < 0.02$. There was no difference between the two dosages.

The EORTC Genito-Urinary Tract Cancer Cooperative Group²⁷ also compared the disease-free interval following prophylactic intravesical chemotherapy of superficial bladder tumors. The drugs compared were thio-tepa, 30 mg/30 cc, VM-26, 50 mg/30 cc, or no therapy. Initiation of therapy was delayed for four weeks following surgery and was continued monthly for eleven months. The recurrence rate was 49.3 per cent in the thio-tepa group, 62.0 per cent in the VM-26 group, and 52.2 per cent in the control group. There was no significant difference among the treatment regimens. There was a difference, however, in the number of tumors per 100 patient months of follow-up. Statistical analysis revealed a lower recurrence rate for those patients receiving thio-tepa compared to those receiving VM-26 or the control.

Since I am concerned that implantation might be a factor in the recurrence rate, it is my preference to initiate intravesical chemotherapy as soon as feasible following transurethral resection or fulguration. If the patient is less than 70 years old and the resection is not extensive, I utilize 60 mg diluted in 60 cc of sterile water for an instillation time of two hours and initiate this the day following resection. Patients older than 70 years receive 30-45 mg. If

Table 4. Results of weekly mitomycin C

DOSE	COMPLETE	PARTIAL	FAIL	TOTAL
30 MG.	1 (17%)	3 (50%)	2 (33%)	6
40 MG.	15 (52%)	10 (34%)	4 (14%)	29
	16 (46%)	13 (37%)	6 (17%)	35

there has been an extensive resection, the instillation may be delayed for three to five days. If there is not significant myelosuppression, therapy is continued weekly for four weeks and then monthly.

During the last couple of years there has been an acceleration in the number of drugs introduced for intravesical chemotherapy. Mitomycin C (MMC) was first reported to be efficacious for intravesical chemotherapy in 1975. Mishina²⁹⁾ treated 50 patients at a dose of 20 mg/20 ml sterile water three times a week. He reported a 44 per cent complete response and 32 per cent partial response rate. Patients with low grade lesions had an 89 per cent response rate compared to 36 per cent for those with high grade tumors. Bracken et al.³⁰⁾ reported the effectiveness of intravesical MMC in 43 patients with Tis or T1 transitional cell carcinoma. This was used as definitive therapy for patients not amenable to transurethral resection. The dose ranged from 20 to 60 mg and was given in eight consecutive weekly doses. The overall response rate was 84 per cent (49 per cent complete, 30 per cent partial and 5 per cent improved). It was felt that the optimal dose was 40 mg.

At the University of Tennessee Center for the Health Sciences I have treated 35 patients with superficial bladder cancer with MMC. This is now twice the number of our original report³¹⁾. Eight weekly doses of 30 mg in 30 cc sterile water were administered to six patients and 29 received 40 mg/40 cc. Seventy per cent of the patients failed thio-tepa. The ages of the 23 men and 12 women ranged from 49 to 97 years (mean 71 years). At least one tumor was histologically confirmed in each patient. If the patient had a solitary lesion, this was not completely excised at the time of biopsy. All patients had one

or more urothelial tumors at initiation of mitomycin C therapy. Six patients had multifocal carcinoma *in situ*. Twelve patients had grade III tumors (CIS=grade III).

The criteria for complete response of an exophytic tumor included the disappearance of endoscopically visible lesions and a negative urinary cytology. If a patient had only CIS, complete response was based on random cold cup biopsy-proven absence of tumor and a negative cytology. A partial response required more than a 50 per cent reduction in the size of all tumors and the absence of new neoplasms. The majority of complete and some of the partial responders received monthly mitomycin C.

The overall response rate was 83 per cent. (Table 4) No tumor was evident in 16 (46 per cent); 13 patients (37 per cent) achieved a partial response. Some of the partial responders only had a positive cytology. The response rate appeared to be somewhat better for those receiving a dose of 40 mg. Interestingly, higher grade tumors responded slightly better than low grade lesions (Table 5). At the twelve week endoscopic session, complete necrosis of previous papillary tumors was frequently observed. Biopsy specimens usually cannot be taken from these firm areas due to intense fibrosis.

Table 5

GRADE/STAGE	NO.	COMPLETE	PARTIAL	FAIL
I-II 0	18	33%	33%	33%
II-III A	17	59%	35%	6%

Although systemic mitomycin C is myelo-suppressive, intravesical treatment did not result in leukocyte or platelet count reduction. This is consistent with the lack of absorption as indicated by serum samples obtained at various periods of time after

MMC instillation. This lack of absorption may be related to the higher molecular weight compared to that of thio-tepa (334 vs 189).

The primary side effect related to mitomycin C was moderate cystitis in four patients and drug-related desquamation of the palmar skin in four. In two patients this palmar reaction was mild and subsided after hydrocortisone cream. In the other two, the rash was severe and accompanied by a macular rash in the perineal region with penile edema. We have performed a series of patch and scratch tests on these patients with concurrent controls and believe that most of the cutaneous reactions are due to a contact dermatitis. Careful cleaning of the hands and perineum following the initial instillation of MMC and all subsequent voidings for the first 24 hours can prevent many of these reactions.

In a similar manner to the studies performed in our laboratory on thio-tepa, we have analyzed the drug-induced urothelial alterations as a result of MMC³². Once again this involved placing mitomycin C into murine bladders and subsequently studying the urinary cytology and histology following cystectomy and multiple step sectioning of the bladders. Cellular abnormalities occurring after mitomycin C were not drug specific and were readily distinguishable from neoplastic changes. Thus it is felt that the drug will not limit the efficacy of urinary cytology in the follow-up of patients treated with MMC.

Mitomycin C may be the most active of the drugs currently under investigation for intravesical chemotherapy. The low incidence of side effects is a major advantage. A prospective trial comparing MMC with thio-tepa for definitive therapy of measurable superficial tumors is currently underway by the National Bladder Cancer Collaborative Group.

Since the carcinogen-induced animal model for bladder cancer has been helpful in selecting drugs for systemic chemotherapy we compared the effectiveness of several intravesically administered drugs on subsequent tumor incidence and tumor size. To mimic the clinical situation, the

carcinogen FANFT was not discontinued during the experiment. Human urinary bladder tumors may be caused by chemical carcinogens and these may persist.

One hundred and six C3H/He female mice were randomly divided into a control group (31 mice) and three treatment groups of 25 each. After 38 weeks on FANFT, intravesical chemotherapy was initiated and consisted of cis-diamminedichloroplatinum II (DDP), 18 mg/kg; mitomycin C, 10 mg/kg; or thio-tepa, 5 mg/kg. These doses represent the highest non-toxic dose utilized by intravesical instillation. Therapy was continued weekly for three weeks; the fourth dose was delayed one week to allow sufficient recovery following the earlier instillations. All of the drugs remained in the bladder for a minimum of 30 minutes which was usually the duration of the intraperitoneal administered anesthesia. All animals were sacrificed during week 46 and the bladders processed for routine light microscopy for identification of the presence of tumor and tumor stage.

The incidence of tumors in the control group was 96 per cent. (Table 6) The tumor incidence in the groups treated with thio-tepa, mitomycin C, and DDP were 71 per cent, 71 per cent and 40 per cent respectively. This reduction was significant in the groups receiving mitomycin C and DDP. The highest percentage of normal bladders was in animals receiving DDP, 60 per cent vs 4 per cent controls, $p < 0.001$.

Table 6. Comparison of intravesical chemotherapeutic agents on the incidence of FANFT-induced bladder cancer

Therapy	No.	Tumors	P
SALINE	28	27 (96%)	-
THIO-TEPA	14	10 (71%)	0.06
MMC	21	15 (71%)	0.04
DDP	16	6 (40%)	0.001

The results reported in this experimental study demonstrate a reduction in the tumor incidence for the treated groups. This appears to correlate with available clinical studies although there has not been a prospective randomized study comparing

thio-tepa to these agents. It should be emphasized, however, that most clinical trials monitor response by endoscopy. Thus thio-tepa eradicates papillary, superficial tumors and reduces the recurrence rate when used for post-resection prophylaxis. These findings might be explained by the toxic effect of this drug. Much of the exophytic, papillary portion of a tumor may be eradicated and the tumor would appear to be destroyed endoscopically thus preventing a transurethral resection. However the appearance of tumor cells in the urine of patients with no endoscopically visible tumors would indicate the lack of drug absorption into the basal layers of the neoplastic urothelium. Thus with time, another visible tumor would develop. This of course would be of benefit to the patient since it might reduce the frequency of endoscopic manipulation and delay, although possibly not prevent, the appearance of new tumors.

It is of interest to review the surveillance data accumulated by the National Bladder Cancer Collaborative Group²⁰. Between 1974 and October 1977, 1071 patients were registered and followed by the Statistical Center; 617 had no prior history of bladder cancer and the institutional diagnosis was confirmed by the central pathology laboratory in 538 of these instances, 259 patients had invasive cancer or had extirpative surgery or radiation therapy after entrance into the protocol, 72 patients had intravesical chemotherapy. Thus 207 patients presented for the first time with transitional cell carcinoma which was confined to the mucosa or lamina propria. 144 of these patients had stage Ta lesions and 63 had T1 tumors. The median follow-up was 39 months. Surprisingly only two percent of those with grade I tumors subsequently developed muscle invasion or metastatic disease whereas 11 per cent of grade II and 45 per cent of grade III tumors subsequently developed muscle invasion. All of those having grade III lesions and progressing did so within two years of the diagnosis. Only 4 per cent of patients harboring a Ta tumor progressed compared to 30 per cent with initial T1

lesions.

Since all of these patients had selected site biopsies at the time of the initial endoscopic session, the likelihood of progression to muscle invasion was compared to the findings of these biopsies. There was a significantly higher chance of progression if moderate or severe dysplasia was found in these biopsies compared to normal or only mild dysplasia.

These data clearly underline the heterogeneity of superficial bladder cancer and emphasize the low likelihood of patients with low grade, stage 0 tumors to subsequently develop a deeply invasive bladder cancer.

Systemic Chemotherapy

The discovery and subsequent evaluation of cis-diamminedichloroplatinum II (DDP) not only altered the uniformly rapid demise for patients with advanced urothelial carcinoma but initiated disease-oriented phase II-III trials of single and combination chemotherapy in TCC. Prior investigations were primarily drug-oriented studies with small numbers of patients with bladder cancer. The few reports that are available lack adequate detail on the extent and location of tumor and the criteria for response. Patients with evaluable parameters such as intra-abdominal or pelvic masses were not analyzed separately from those with strictly measurable lesions, e.g. pulmonary nodules, cutaneous or subcutaneous masses, and liver metastases. Since the primary tumor may respond differently from metastases and since the accuracy of evaluation of tumor size depends on location, this information is critical to the accurate assessment of the drug's activity.

The use of cis-platin in human bladder cancer was spurred by a series of experiments in the FANFT-induced transitional cell carcinoma model which identified it as one of the most effective drugs inhibiting growth of both transplanted and primary tumors³³⁻³⁴. The first major clinical evidence of its efficacy in human transitional cell carcinoma was provided by Yagoda et al.³⁵. They observed a 37 per cent objective partial response rate; 50 per cent in

previously untreated patients. The average duration of response was five months.

I have now treated 39 patients with locally advanced or metastatic urothelial carcinoma with DDP. There were 26 males and 13 females. The average age was 66 (range 41–81). Twenty-two of the patients had metastatic disease and 17 had their disease confined to the pelvis. The dose utilized in all patients was 70 mg/M² every three to four weeks. Only one of these patients had prior chemotherapy.

Mannitol-induced diuresis was uniformly instituted to reduce the potential nephrotoxicity related to DDP. All patients received a 60 minute infusion of 500 cc of 5 per cent dextrose in one half normal saline followed by 12.5 mg mannitol by intravenous push prior to receiving DDP. The DDP was infused over 15 minutes. Following the DDP an additional 500 cc of 5% dextrose in one half normal saline was infused during the next 60–90 minutes.

All patients received a minimum of two doses of DDP. Responses were usually evident within six weeks. A complete response was defined as complete disappearance of all tumor. A partial response required a 50 per cent or more reduction in the sum or the products of two perpendicular diameters of the tumor and no new lesions or increase in the size of any existing lesions. Patients with tumor confined to the bladder or pelvis were evaluated by cystoscopy (if the bladder was present), bimanual examination under anesthesia, and usually a CAT scan.

None of the patients achieved a complete response (Table 7). Eleven (28 per cent) achieved a partial response while an additional 16 (41 per cent) remained stable for a minimum of two months. The

average duration of response for both the partial responders and those remaining stable was six months.

Twenty-two patients had bidimensionally measurable metastatic disease. Seven (32 per cent) achieved a partial response and an equal number remained stable. The response rates for the 17 patients whose disease was confined to the bladder or pelvis at the time of initiation of chemotherapy were also analyzed separately. Four (23 per cent) achieved a partial response while nine (54 per cent) were stabilized. The average response duration was five and eight months respectively.

Utilizing the life table method, the probability of surviving six months for patients receiving a partial response, remaining stable, or progressing was 78 per cent, 84 per cent, and 17 per cent respectively. Thus stabilization of the disease appeared to be as efficacious in regard to survival as those achieving an objective regression. In addition, the probability of surviving six or twelve months for patients with metastatic disease was approximately 50 per cent compared to 85 per cent for those whose tumor was confined to the bladder or pelvis. At twelve months these figures were 29 and 61 per cent respectively.

Efforts to further improve upon the results achieved by DDP alone have prompted trials employing combination chemotherapy. In general the results from our murine studies indicate a slightly greater reduction in tumor with the addition of cytoxan and/or adriamycin to DDP when compared to cis-platin used alone. Clinical reports indicate a 2–3 month longer response duration with a two or three drug regimen; however, the response rates are approximately the same as achieved with DDP alone. Toxicity is increased when these myelosuppressive drugs are added to DDP. Yagoda³⁶⁾ found the combination of cytoxan + DDP to yield an identical response rate to that achieved by DDP alone. Similar results were observed by these investigators with a combination of DDP and adriamycin. Samuels et al.³⁷⁾ observed an objective response rate of 41 per cent (17/41) when combining cytoxan, adria-

Table 7. CIS-platin in advanced urothelial cancer

	No.	%	Ave. Duration
COMPLETE RESPONSE	-	-	-
PARTIAL RESPONSE	11	28	6
STABLE	16	41	6
PROGRESSION	12	31	-
TOTAL	39		

mycin and high dose cis-platin. It should be indicated, however, that among these responses were seven complete responses.

Although nephrotoxicity resulting from DDP is a potentially serious complication, the routine use of hydration and mannitol-induced diuresis has largely obviated this problem. Almost all of the patients who had a serum creatinine rise significantly under therapy with DDP had either a solitary kidney or significant ureteral obstruction.

The National Bladder Cancer Collaborative Group recently completed a prospective randomized protocol to compare the efficacy of cis-platin, 70 mg/M² IV every three weeks to cis-platin+cyclophosphamide, 750 mg/M² given in the same intervals³⁸⁾. Response was assessed at the nine week interval following three courses of chemotherapy. Patients were stratified into four groups depending on whether they had measurable or evaluable disease as well as upon their performance status. Measurable disease was classified as pulmonary nodules, enlarged lymph nodes or cutaneous masses which were measurable in two dimensions. None of the patients received prior systemic chemotherapy and at least four weeks must have elapsed since prior radiation therapy. Hematologic status and renal function were required to be normal. 127 patients were accessioned into the protocol and 105 were evaluable for response.

Ten of 49 patients (20.4 per cent) receiving cis-platin alone had an objective response compared to only seven of 56 patients (12.5 per cent) who received the combination. There was no statistically significant difference between these response rates. There were complete responses evident in both treatment categories, four receiving the single agent and two the combination. Approximately one third of the patients in each group were stabilized as a result of this chemotherapeutic regimen. The median time to response was 73 days.

Evaluation of response as a function of performance status indicated that patients with a better performance status receiving DDP alone had a 23.3 per cent complete or partial response rate compared to 15.8 per

cent of those in the lower performance status category. The respective response rates for patients receiving the combination were 15.2 per cent and 8.7 per cent respectively. There was no significant difference between the response rates for those having either measurable or evaluable disease.

Evaluation of survival indicated no difference between the two treatment regimens. There was a far greater likelihood of surviving six months for patients having either an objective response or remaining stable with no apparent difference in survival between these response categories.

It is evident from the above review of our results with cis-platin and those of other single investigator or cooperative groups that there is a need to greatly improve chemotherapy for patients with advanced urothelial carcinoma. As part of our continuing studies to screen prospective anti-tumor drugs for activity in the FANFT-induced transitional cell carcinoma in murine model, we have recently evaluated VP16-213.

Etoposide or VP16-213 is a semi-synthetic derivative of podophyllotoxin. Its mode of action consists of metaphase arrest and premitosis inhibition. Several phase II trials have indicated that among the disease categories for treatment with VP16 showing promise is urinary bladder cancer. The number of patients, however, with bladder cancer receiving this agent were few. These reports also lack sufficient detail on the extent of tumor and the criteria for response to be meaningful. The maximum tolerated dose of VP16 was determined to be between 40 and 50 mg/kg.

In an initial series of studies the transplantable murine bladder cancer, MBT2, was utilized. A single cell suspension of the tumor was prepared and 7.5×10^4 viable cells were placed IM in the left hind limb of 64 C3H/He mice. The animals were randomly divided into a control and four treatment groups. Therapy was initiated on day seven and continued weekly for three doses. The therapeutic regimens consisted of: VP16, 50, 55 or 60 mg/kg or DDP, 6 mg/kg. Drugs were given by the intraperitoneal route.

A second study involved 44 C3H/He mice divided into a control group of 20 and two treatment groups of 12 mice each. The doses of VP16 and DDP were 50 and 6 mg/kg respectively.

All mice were examined daily to determine the onset of palpable tumors. Tumor growth was determined by biweekly measurement of tumor diameter and an average computed. The increase in life span (ILS) of treated mice was compared to that of the untreated tumor-bearing control group. The percent ILS was calculated by subtracting the median survival time (MST) of the control group from the treated group divided by the MST of the control $\times 100$. The ILS takes into account deleterious effects resulting from drug toxicity.

Tumor incidence was 100 per cent in all of the groups. DDP and each of the three doses of VP16 produced a significant reduction in the mean tumor diameter as measured on day 23. Although the higher doses of VP16 yielded somewhat greater inhibition, the ILS was highest in the mice receiving a dose of 50 mg/kg. The ILS of mice receiving this dose of VP16 was superior to the group receiving DDP. In the second study, once again VP16 and DDP demonstrated significant reduction in mean tumor diameter compared to the control group. The ILS of those receiving DDP was superior to mice being treated with VP16.

The effect of VP16 and DDP was also evaluated in a long-term study in 111 female C3H/He mice fed a diet containing 0.1 per cent FANFT for 39 weeks. Once again the animals were randomly divided into a control group (31) and four treatment groups of 20. Therapy consisted of VP16, 50 mg/kg; DDP, 6 mg/kg; VP16, 40 mg/kg + DDP, 4 mg/kg; or VP16, 50 mg/kg + DDP, 6 mg/kg. Drugs were given IP in a volume of 0.1 cc for four weeks. All of the bladders of the surviving mice were excised at week 46. The bladders were weighed and step histologic sections obtained to determine tumor incidence and stage.

The mice receiving the lower dose of the DDP-VP16 combination had a significant

reduction in the incidence of tumors compared to the controls (50 per cent vs 96 per cent). The primary difference was the lack of carcinoma *in situ* in the treatment group. The only group having a significant reduction in the mean log bladder weight were those receiving the combination of DDP + VP16, 50 mg/kg.

In this long-term study utilizing primary FANFT-induced bladder tumors, mice receiving DDP had a reduction of tumor incidence compared to the control group while those receiving VP16 did not have such a reduction. Mice receiving the low dose DDP-VP16 combination had a significant reduction in tumor incidence while the higher dose combination had a significant reduction in the mean bladder weight. Thus the antineoplastic activity of this combination was more effective than either of the drugs utilized alone.

REFERENCES

- 1) Barnes RW, Dick AL, Hadley HL and Johnston OL: Survival following transurethral resection of bladder carcinoma. *Cancer Res* **37**: 2895~2897, 1977
- 2) Greene LG, Hanash KA and Farrow GN: Benign papilloma or papillary carcinoma of the bladder? *J Urol* **110**: 205~207, 1973
- 3) MacKenzie N, Torti FM and Faysa L: Natural history of superficial bladder tumors. *Proc Amer Assoc Cancer Res* **22**: 198, 1981
- 4) Heney NM, Ahmed S, Flannigan MJ, Frable J, Corder MP and Hafermann MD: Superficial bladder cancer: Progression and recurrence. Presented at AUA Annual Meeting, May 10-14, Boston, Massachusetts, 1981
- 5) Melicow MM: Histological study of vesical urothelium intervenign between gross neoplasms in total cystectomy. *J Urol* **68**: 261~279, 1952
- 6) Farrow GM, Utz DC and Rife CC: Morphological and clinical observations of patients with early bladder cancer treated with total cystectomy. *Cancer Res* **36**: 2495~2501, 1976
- 7) Soto EA, Friedell GH and Tiltman AJ: Bladder cancer as seen in giant histologic sections. *Cancer* **39**: 447~455, 1977
- 8) Soloway MS, Murphy WM, Rao MK and Cox CE: Serial multiple-site biopsies in patients with bladder cancer. *J Urol* **120**: 57~59, 1978
- 9) Murphy WM, Nagy GK, Rao MK, Soloway MS, Parija GC, Cox CE and Friedell GH: "Normal" urothelium in patients with bladder cancer. *Cancer* **44**: 1050~1058, 1979

- 10) Wolf H and Hojgaard K: Urothelial dysplasia in random mucosal biopsies from patients with bladder tumors. *Scand J Urol Nephrol* **14**: 37~41, 1980
- 11) McDonald DF and Thorson T: Clinical implications of transplantability of induced bladder tumors to intact transitional epithelium in dogs. *J Urol* **75**: 690~695, 1956
- 12) Weldon TE and Soloway MS: Susceptibility of urothelium to neoplastic cellular implantation. *Urology* **5**: 824~827, 1975
- 13) Soloway MS and Masters S: Urothelial susceptibility to tumor cell implantation - influence of cauterization. *Cancer* **46**: 1158~1163, 1980
- 14) Soloway MS: Intravesical and systemic chemotherapy of murine bladder cancer. *Cancer Res* **37**: 2918~2929, 1977
- 15) Hollands FG: The results of diathermy treatment of villous papilloma of the bladder. *Br J Urol* **22**: 342~375, 1950
- 16) Hinman F Jr: Recurrence of bladder tumors by surgical implantation. *J Urol* **75**: 695, 1956
- 17) Soloway MS: Rational for intensive intravesical chemotherapy for superficial bladder cancer. *J Urol* **123**: 461~466, 1980
- 18) Veenema RJ, Dean AL Jr, Roberts M, Fingerhult B, Chowdhury BK and Tarassoly H: Bladder carcinoma treated by direct instillation of thio-tepa. *J Urol* **88**: 60~63, 1962
- 19) Abbassian A and Wallace DM: Intracavitary chemotherapy of diffuse non-infiltrating papillary carcinoma of the bladder. *J Urol* **96**: 461~465, 1966
- 20) Edsmyr F and Bowman J: Instillation of thio-tepa in vesical papillomatosis. *Acta Radiol: Therapy physics biology* **9**: 395~400, 1970
- 21) Koontz WW Jr, Prout GR, Smith W, Frable WJ and Minnis JE: Use of intravesical thio-tepa in management of non-invasive carcinoma of the bladder. *J Urol* **125**: 307~312, 1981
- 22) Murphy WM, Soloway MS and Lin CJ: Morphologic effects of thio-tepa on mouse urothelium. *Acta Cytol* **21**: 701~704, 1977
- 23) Murphy WM, Soloway MS and Lin CJ: Morphologic effects of thio-tepa on mammalian urothelium: Changes in abnormal cells. *Acta Cytol* **22**: 550~554, 1978
- 24) Murphy WM and Soloway MS: The effect of thio-tepa on developing and established mammalian bladder tumors. *Cancer* **45**: 870~875, 1980
- 25) Burnand KG, Boyd PJR, Mayo ME, Shuttleworth KED, Lloyd-Davies RW: Single dose intravesical thio-tepa as an adjuvant to cystodiathermy in the treatment of transitional cell bladder carcinoma. *Br J Urol* **48**: 55~59, 1976
- 26) Byar D and Blackard C: Comparison of placebo, pyridoxine, and topical thio-tepa in preventing recurrence of stage I bladder cancer. *Urology* **10**: 556~561, 1977
- 27) Schulman C, Sylvester R, Robinson M, Smith P, Lachand A, Denis L, Pavone-Macaluso M, DePauw M and Staquet M: Adjuvant therapy of T1 bladder carcinoma. In Bonadonna, G., Mathe, E.G. and Salmon, S.E. (ed) *Recent results in cancer research*, vol. 68, Springer-Verlag, Berlin, pp.338~345, 1979
- 28) England HF, Paris AMI and Blandy JP: Intravesical thio-tepa as adjuvant to cystodiathermy in multiple recurrent superficial bladder tumors. In Oliver, R.D.S., Hendry, W.S., Bloom, H.J.G. (ed.) *Bladder cancer - principles in combination therapy*, Butterworths, London, pp.67~73, 1981
- 29) Mishina T, Oda K, Murata S, Ooe H, Mori Y and Takahashi T: Mitomycin C bladder instillation therapy for bladder tumors. *J Urol* **114**: 217~219, 1975
- 30) Bracken RB, Johnson DE, Von Eschenback AC, Swanson DA, DeFuria MD and Crooke ST: Role of intravesical mitomycin C in management of superficial bladder tumors. *Urology* **16**: 11~15, 1980
- 31) Soloway MS, Murphy WM, DeFuria MD, Crooke S and Finebaum P: The effect of mitomycin C on superficial bladder cancer. *J Urol* **125**: 646~648, 1981
- 32) Murphy WM, Soloway MS and Crabtree WN: The morphologic effects of mitomycin C in mammalian urinary bladder. *Cancer* **47**: 2567~2574, 1981
- 33) Soloway MS: Single and combination chemotherapy for primary murine bladder cancer. *Cancer* **36**: 333~340, 1975
- 34) Soloway MS and Murphy WM: Experimental chemotherapy of bladder cancer - systemic and intravesical. *Semin Oncol* **6**: 166~183, 1979
- 35) Yagoda A, Watson RC, Gonzalez-Vitale JC, Grabstald H and Whitmore WF: Cis-dichlorodiammineplatinum (II) in advanced bladder cancer. *Cancer Treat Rep* **60**: 917~923, 1976
- 36) Yagoda A: Phase II trials in bladder cancer at Memorial Sloane-Kettering Cancer Center, 1975-1978. In Johnson, D.E. and Samuels, M.L. (ed) *Cancer of the genitourinary tract*. New York, Raven Press, 1979, pp.107~119
- 37) Samuels ML, Moran ME, Johnson DE and Bracken RB: CISCA combination chemotherapy for metastatic carcinoma of the bladder. In Johnson, D.E. and Samuels, M.L. (ed) *Cancer of the genitourinary tract*. New York, Raven Press, 1979, pp.101~106
- 38) Einstein A, Soloway MS, Corder M, Bonney W and Koombis J: Diaminedichloroplatinum (DDP) vs DDP+cyclophosphamide for metastatic bladder carcinoma. *The National Blad-*

der Cancer Collaborative Group A (NBCCGA)
Study. Proc Am Assoc Cancer Res 22: 461,

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和文抄録

CONCEPTS IN THE TRETMENT OF BLADDER
CANCER—CLINICAL AND EXPRIMENTAL

Mark S. SOLOWAY, M. D.

*Professor, Department of Urology**University of Tennessee center for the Health Sciences*

膀胱癌患者に対する適切な治療方法を決めるにはその腫瘍の性質、すなわち悪性度、浸潤度および多発性などについての正確な評価が重要であり、またその患者の予後は腫瘍浸潤度により大きく左右される。

膀胱腫瘍の評価に重要な内視鏡検査、内視鏡的生検と病理組織学的検査および尿細胞診の問題点について考察した。

近年、表在性膀胱腫瘍の手術後の高い再発頻度が問題となっているが、この再発の病因は new occurrences と true recurrences の2つに大別され、前者は腫瘍の多中心発生に、後者は手術時の腫瘍細胞の膀胱内播種によると考えられ、とくに true recurrences に

ついては動物実験によって腫瘍細胞が電灼部位に播種することを証明した。

膀胱腔内化学療法は治療としてまた再発予防として、近年広く施行されているが、Thiotepa, MMC および CDDP についてその臨床および動物実験における治療成績について述べた。

全身化学療法について、近年優れた治療成績が報告されている CDDP を中心に検討を行ったが、CDDP を中心とする多剤併用療法は現時点では余り有効とはいえない。しかし動物実験では CDDP と VP 16 の併用が良い成績を示している。