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Approaches to the treatment of bladder cancer at Stanford

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Summary. The treatment of bladder cancer is one of the most active areas of clinical cancer research. The use of new classes of intravesical agents, such as the interferons, and anlogues of effective intravesical chemotherapies, such as epirubicin, the 4-epimer of doxorubicin, show promise of controlling the sequela of this common urologic problem. In metastatic transitional cell carcinoma, the CMV regimen holds promise of palliation for many and or long-term remission for some patients with advanced bladder cancer.

Introduction

In this paper I have taken the opportunity to outline the approaches we have utilized at Stanford and the Northern California Oncology Group (NCOG) in our efforts to understand the natural history and the effect of therapeutic interventions on the natural history of bladder cancer. Many of these approaches are investigational, and many of the results are still preliminary. It is important, therefore, not to misconstrue this paper as a list of treatment recommendations, but rather to accept it as an outline of our current and proposed investigations in bladder cancer.

Each major stage of bladder cancer is briefly described in terms of the current issues and controversies that relate to natural history and treatment of the disease and of the rationale which led to each particular investigative approach.

Superficial bladder cancer

Introduction

Superficial bladder cancer, that disease confined to the mucosal and submucosal surfaces of the bladder, accounts for nearly 70% of all newly diagnosed cases of bladder cancer in the United States [30]. This high incidence, combined with the requirement for frequent follow-up to evaluate and treat recurrent disease, means that the management of superficial bladder cancer is major fraction of the care delivered to patients with urologic tumors. Superficial cancers are of two general types. The first are discrete tumors, usually papillary and of low grade, which present clinically in most patients as hematuria. This is the predominant form of superficial bladder cancer. Low-grade papillary transitional cell neoplasms can usually be treated adequately with transurethral resection alone (TURBT). That is to say, it is unusual to have recurrent tumor at the site of a previous resection. However, the biologic propensity of the patient to develop new tumors in the bladder cannot be approached surgically. The impetus to prevent new tumor occurrence (regardless of the pathophysiology of new tumor growth) has stimulated the development of intravesical chemotherapeutic approaches for these low-grade tumors. The second type of superficial tumor is carcinoma in situ (CIS), a high-grade malignancy which presents with dysuria and frequency (it is often asymptomatic). The primary therapeutic strategy in CIS is different than in low-grade papillary tumors. The frequently diffuse nature of the urothelial disease makes primary surgical management problematic except by total cystectomy; intravesical chemotherapy is therfore often used [18]. In both cases, however, critical evaluation of treatment results requires assessment of the outcomes listed in Table 1.

Although a minority of patients with muscle-invasive carcinomas have clinically apparent antecedent superficial cancers, all patients with superficial bladder cancer have the potential to develop an invasive cancer, a potentially lethal sequela. Thus, although a number of the outcomes in Table 1 may be beneficial to the patient, the major therapeutic aim in the treatment of bladder cancer is to prevent the development of tumors which invade the bladder wall.

Table 1. Questions addressed in intravesical chemotherapeutic trials

Question	Analysis of
Did a tumor recur?	Recurrence
When did it recur?	Recurrence/time
How many recurred?	(Recurrence) × (Tumor no.)/Time
How many with stage or grade advancement (without muscle invasion)?	Progression
How many invaded?	Invasion
How many died of bladder cancer?	Disease-free survival

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Prognostic factors for invasion in superficial bladder cancer

To assess which characteristics of patients and their tumors predict for the eventual development of muscle-invasive tumor, we evaluated 252 patients who were treated at Stanford Univeristy with transurethral resection alone for bladder cancer. Tumor location within the bladder, tumor grade and stage, patient history of smoking, and other variables were assessed. Although both stage and grade of the tumor predicted for the propensity to develop invasive cancer, when their overlapping contributions were evaluated separately using multivariate analysis, grade of tumor was the primary factor predicting for invasive cancer [3, 4].

We next wanted to find whether the risk of developing invasive cancer increased as the number of recurrences increased. If this is true, patients with multiple episodes of superficial recurrence should be followed up more closely. To assess this risk, we evaluated the probability of invasive disease for the group at risk for second, third, fourth, and subsequent recurrences. Surprisingly, there was no greater risk of development and invasive bladder cancer in the group with six or more previous superficial recurrences than in groups with fewer recurrences. Thus, the risk of development of invasive cancer at any point in the patients disease can be viewed in a stochastic sense as independent of prior superficial recurrence, much in the same way as the result of a coin toss is independent of the previous tosses [19, 32].

Chemotherapeutic approaches to intravesical disease

Intravesical toxicity of mitomycin C and thio-TEPA

Many chemotherapeutic agents have been used to alter the natural course of superficial bladder cancer [18, 30, 31]. Intravesical chemotherapy has been used to treat overt cancer, and has also been used to prevent recurrence after cystoscopic resection. Among the more effective, intravesical chemotherapeutic agents are thio-TEPA, mitomycin C, bacille Calmette Guérin (BCG), doxorubicin (adriamycin) and, most recently, epirubicin, the 4'-epimer of doxorubicin [30]. The Northern California Oncology Group, in a randomized trial, has studied the efficacy and toxicity of adjuvant intravesical mitomycin C and thio-TEPA. Thio-TEPA was used at a dose of 60 mg dose, mitomycin C at a dose of 20mg. Instillation was performed weekly for 8 weeks, than monthly for 2 years. Although effiicacy data are still not available, toxicity data have been reported in abstract form. Thus far, although the study is not complete, no differences in local (or systemic) toxicity have been observed. Dsysuria and dermatitis occurred infrequently in both groups; myelosuppression was not observed in either group [37].

Interferon in superficial bladder cancer

The interferons have been utilized to a limited extent in the treatment of superficial bladder cancer. Small numbers of patients have been treated with local injections around tumors [12] and with systemic administration [2, 28].

In a cooperative study organized by the Northern California Oncology Group, we have evaluated the effects of alpha-2 interferon in the treatment (not prophylaxis) of superficial transitional cell carcinoma, both papillary cancers and carcinoma in situ. The rationale for topical treatment with the interferons is strong, and the results with intraperitoneal treatment of ovarian cancer have been encouraging. The results of this study have not been published, but a preliminary evaluation has been reported in abstract form [32]. In this phase I study, escalating doses of interferon were utilized, from 50 million to 1000 million units instilled intravesically for 2 h in 30 cm^3 of normal saline. Complete responses have been observed in CIS and papillary tumors in patients with refractory disease. Minimal local and systemic toxicity have been noted. Both the optimal dosage and the efficacy relative to other intravesical treatments will need to be assessed in subsequent trials.

Adriamycin and its analogues in the treatment of superficial cancer

The anthracyclines have activity against superficial bladder cancer, both as a definitive therapy of established disease and in the prophylaxis against recurrence in those patients at high risk of recurrence after transurethral resection. Doxorubicin (adriamycin) has been extensively utilized in superficial bladder cancer [4–8, 16, 17, 23–26]. Relevant data are summarized in Tables 2 and 3. Epirubicin, the 4'-epimer of doxorubicin, also has excellent activity when used intravesically, according to some preliminary reports exceeding the activity of doxorubicin [20, 34–36].

Table 3. Doxorubicin as prophylactic therapy

Study	No. of patients in study	Follow-up period (months)	% With recurrence	
			Control	Treated
Banks et al. [1]	13	21	–	38
Jacobi et al. [14]	30	22	87	33
Schulman et al. [27]	82	12+	–	39
Jacobi et al. [13]	64	9–19	–	44
Horn et al. [11]	12	9	25[a]	14

[a] Control group received intravesical thio-TEPA therapy

Table 2. Doxorubicin as definitive therapy for superficial bladder tumors

Study	No. of patients	CR (%)	PR (%)	CR + PR (%)	Failures (%)
Pavone-Macaluso et al. [25, 26]	5	0	3 (60)	3 (60)	2 (40)
Ozaki [24]	80	22 (27)	35 (44)	57 (71)	23 (29)
Nijima [22]	194	39 (20)	72 (37)	111 (57)	83 (43)
Edsmyr et al. [3]	53	37 (70)	5 (9)	42 (79)	11 (21)
Jaske [15]	15	10 (66)	0	10 (66)	5 (34)
Total	347	108 (31)	115 (33)	223 (64)	124 (37)

CMV in the treatment of advanced bladder cancer

A major advance in the treatment of advanced bladder cancer has been the demonstration that cisplatin and methotrexate, the two most active single agents, can be giiven in combination with acceptable toxicity. This has permitted investigation of these two drugs in a variety of combination chemotherapies for this disease [9, 29]. At Stanford, a combination of cisplatin, methotrexate and vinblastine has been developed (CMV). This regimen produced a number of complete responses (29% in the initial series) [10]; a number of the patients attaining complete response (CR) in this study remain disease-free after as long as 5 years. The administration of CMV is outlined in Tables 4–6. The effective administration of CMV requires a great deal of care to ensure administration of the highest possible dose while limiting the risk of nephrotoxicity.

An important aspect of the response to CMV chemotherapy has been the excellent activity of CMV chemotherapy against disease in the bladder. Among 17 patients with disease in the bladder at the initiation of CMV chemotherapy, 11 (65%) had a CR in the bladder. This included 6 or 12 treated with CMV alone and 5 of 5 treated with CMV plus irradiatiion [21]. This latter group, in particular, suggests that combined approaches of CMV and radiation therapy should be tested in patients with advanced but localized bladder cancer.

Table 4. CMV chemotherapy for transitional cell carcinoma

CMV	Day 1 (mg/m^2)	Day 2 (mg/m^2)	Day 8 (mg/m^2)	Cycle
Methotrexate	30		30	
Vinblastine	4		4	21 days
Cisplatin		100		

Table 5. Dose reduction for CMV chemotherapy: hematologic toxicity. Percentage of initial calculated dose of methotrexate and vinblastine (to be used to adjust for hematologic status before each cycle)

WBC	Platelets			
	≥ 150 000	100 000 149 000	75 000 99 999	< 75 000
≥ 35000	100%	100%	50%*	0*
3000–3499	100%	100%	50%*	0*
2500–2999	50%*	50%*	0*	0*
< 2500	0%*	0*	0*	0*

* If WBC ≤ 1000 (and/or polycytes ≤ 500) or if platelets ≤ 50 000 during previous cycle but counts have returned to "dosing levels", administer only 80% of dose given in cycle before
If WBC ≥ 3000 and platelets ≥ 100 000, treat on schedule at dose specified in table
If the dose on day 1 of subsequent cycle (day 21) falls into the 0–50% range (*), delay initiation of cycles up to 1 week (day 28). If counts are still in the 50% range at week 4 (day 35), treat at 50% dose

Table 6. Dose reduction for CMV chemotherapy: renal toxicity

A. Methotrexate

Do not give methotrexate on day 8 if any of the following ocur (vinblastine can still be given):

1. Creatinine clearance falls by greater than 30 cm^3/min compared with the day 1 value
2. The absolute day-8 value is less than 45 cm^3/min
3. Serum creatinine is 2.0 mg% on day 8, regardless of creatinine clearance
4. Rescue MTX if stomatitis or platelets < 75 000

B. Cisplatin

Percent of initial calculated dose of cisplatin (to be used to adjust for renal status for each cycle)

Creatinine clearance (cm^3/min)	% of calculated cisplatin dose
> 60 cm^3/min	100%
45–60 cm^3/min	50%
< 45 cm^3/min	0

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