Cancer Chemother Pharmacol (1983) 11 (Suppl): S 5–S 8

Cancer Chemotherapy and Pharmacology

Intravesical chemotherapy in the United States

An overview

Joseph T. Spaulding

909 Hyde St., Suite 222, San Francisco, CA 94109, USA

Summary. *Intravesical chemotherapy has been widely employed in this country as part of the treatment strategy for clinically localized bladder cancer. Although surgery remains the principal therapeutic modality, intravesical agents are increasingly being considered as adjuncts and as salvage or prophylactic therapy for polychronotopic superficial disease. Instillation treatment is first-line therapy for diffuse in situ carcinoma.*

Several compounds have been subjected to intravesical trials in this country, but thio-TEPA has been most extensively studied. More recently mitomycin C and Adriamycin have been utilized following encouraging preliminary reports from abroad. BCG, a biologic agent, has also stimulated interest and current trials. Phase I–II studies with intravesical interferon have been initiated.

While the potential role for intravesical therapy is becoming clear, additional trials to test new agents, compare current agents, and refine dose, concentration, volume, and contact time are indicated.

Intravesical chemotherapy has been widely used in this country as part of the treatment strategy for superficial bladder cancer. Although surgery remains the principal therapeutic modality, intravesical agents are increasingly being considered for primary or prophylactic therapy in polychronotopic disease. Instillation treatment is now often the initial therapy for diffuse in situ carcinoma.

While the basic rationale for intravesical instillation of cytotoxins in bladder cancer has been evident for several decades, it is only within the past 20 years that agents with appreciable activity and tolerable toxicity have become available. Early experience with several different compounds, including silver nitrate, trichloracetic acid, podophyllin, and clorpactin was disappointing. Subsequent trials with radioactive isotopes were also unrewarding and frequently associated with bladder fibrosis, contracture, and hemorrhage [39].

In 1961 Johnes and Swinney [23], and in 1963 Veenema et al. [40] described the antitumor activity of intravesical thio-TEPA. Since that time, several other chemotherapeutic agents have been tested [14, 36], but appreciable experience in this country is available only with thio-TEPA, mitomycin C, Adriamycin, and recently BCG.

Thio-TEPA

Thio-TEPA is a cell-cycle-nonspecific alkylating agent which is chemically related to nitrogen mustard. It is a low-molecular-weight compound that can be absorbed through the bladder and may result in systemic toxicity. Myelosuppression, manifest primarily as leukopenia and thrombocytopenia, can be acute or chronic, seems to be dose-related, and occurs sufficiently frequently (12%–26%) to make routine hematologic monitoring mandatory [19, 24, 31]. As with other agents, absorption is enhanced in bladders containing tumors, following radiotherapy, in the presence of inflammation, and after endoscopic resection. Local toxicity in the form of chemical cystitis is reversible but bladder contracture, allergic phenomena, and sterility have also been reported [20, 41]. The drug is commonly administered as a 30–60-mg dose in a 1-mg/cm^3 concentration, and held in the bladder for 2 h. The dosage schedule depends upon the intent of the therapy.

Thio-TEPA is generally held to be active in eliminating existing tumors. Following six to eight weekly intravesical instillations of thio-TEPA, approximately one-third of patients will experience complete clearance of tumor, and another third, a partial clearance [14, 23, 24, 41]. The response rate is independent of tumor grade, superficial stage, and gross morphology. Large tumors (>4 cm) and multiple tumors (≥ 4) respond to a lesser degree [24].

The value of thio-TEPA in prevention of recurrent tumors has been more difficult to assert [2, 11, 43]. Recently, the National Bladder Cancer Collaborative Group A initiated a study designed to reconfirm the primary activity of thio-TEPA and to carefully assess its usefulness as a prophylactic agent [24]. Two dosage levels were studied (30 and 60 mg) and an untreated control group was included in the prophylactic phase. Of the 95 patients with stage O–A carcinoma of the bladder, 45 were cystoscopically tumor-free after two courses, though 15 of these remained cytologically positive. The 30- and 60-mg doses were equally effective.

In the prophylactic phase of this cooperative group study, the dosage schedule required monthly instillations for a maximum of 2 years. The study groups were comparable with respect to important tumor-related variables such as antecedent tumor frequency, tumor multiplicity, and interval from last tumor. At the last report, early analysis required statistical projections, which nevertheless demonstrated a significant benefit from prophylactic thio-TEPA irrespective of dose (30 or 60 mg). At 12 months only 40% of control patients were free of recurrence, as against 66% of those receiving thio-TEPA. Patients who had participated in the therapeutic phase of this study and had exhibited a complete response did particularly well with prophylactic thio-TEPA (100% disease-free at 12 months).

In another controlled study [8], under the direction of the Veterans Administration Cooperative Research Group, thio-TEPA significantly decreased the frequency of recurrences compared with pyridoxine and placebo, although the number of patients in whom disease recurred was not reduced and the disease-free interval was not lengthened.

Short-term thio-TEPA prophylaxis immediately after resection seems to diminish recurrence regardless of the particular dosage schedule, and presumably acts by eliminating the implantation of malignant cells on the urothelial surface traumatized during endoscopic therapy [7, 13, 34]. Gavrell et al. [16] initiated prophylactic thio-TEPA treatment in the immediate postoperative period, decreasing the recurrence rate without appreciable toxicity.

Intravesical thio-TEPA has been suggested [42] as an adjunct to prevent pelvic and wound implantation following open-bladder surgery for carcinoma, a largely unexplored role for intravesical agents.

Mitomycin C

Mitomycin C is an antitumor antibiotic isolated from *Streptomyces caespitosus* and, like thio-TEPA, it functions as an alkylating agent. Its molecular weight is 334, which is felt to account for the lack of measurable absorption and systemic toxicity. The incidence of vesical irritation ranges from 6% to 32%, and this can be sufficiently severe to cause termination of the planned treatment course [10, 26, 37]. Contact dermatitis has been described, which is avoided by careful washing of hands and genitalia [32]. Primary activity has been demonstrated at doses ranging from 20 to 60 mg instilled in 1-mg/cm^3 concentrations weekly for 8 weeks. The objective response rate ranges from 67% to 86%, complete response rates being consistently about 45% [5, 10, 26, 32, 37]. Responses were evident in thio-TEPA failures, though at a lesser rate [37]. Prophylactic activity of mitomycin C has been suggested [9] and is the subject of a phase-III comparison with thio-TEPA recently initiated by the Northern California Oncology Group.

Doxorubicin

Doxorubicin (Adriamycin) is an antitumor antibiotic of the anthracycline group, which has been the focus of studies conducted by the European Organization for Research on the Treatment of Cancer (EORTC) [39]. A large molecule (molec. wt. 552), doxorubicin has been essentially free of systemic effects other than occasional allopecia [3, 12, 35]. Local symptoms of irritation and hematuria appear to be dose-related, can be frequent (22%) and severe, but are usually mild and reversible [3, 12, 15, 35]. Measurable diminished capacity due to bladder wall fibrosis has been documented, but has not as a rule been clinically evident [12, 22]. The usual dose employed ranges from 50 to 80 mg, instilled at 1–2 mg/cm^3 concentration with a contact time of 1–2 h. Both primary and prophylactic activity have been noted [1, 12, 22, 35].

Published experience with this agent in the United States is limited. Garnick et al. reported [15] a 61% complete response rate, cystoscopically and cytologically, to primary doxorubicin instillation in 18 patients with stage O–A, low- and high-grade tumors. Therapy was initiated with 60 mg Adriamycin instilled in 40–50 cm^3 and retained for 1 h every 3 weeks for 2 months. Doses were escalated to 90 mg and the frequency of instillation was tapered over the course of 1 year.

In 1977 Banks et al. [3] reported the results of a predominantly prophylactic study of intravesical doxorubicin in 13 patients. Starting 2 weeks after surgical clearance of the bladder, each month 50 mg doxorubicin was instilled in a volume of 150 cm^3 and retained for 30 min. Cytology that was positive before the instillation converted to negative in 10 of 12 patients, and one of two patients with incompletely resected papillomatosis had complete clearance. Eight of the 13 patients exhibited no recurrence although the median follow-up was only 10 months. No local or systemic toxicity was noted.

A controlled prophylactic study [44] was conducted at the Mayo Clinic, involving 90 consecutive patients who randomly received intravesical saline, 50 mg Adriamycin, or 60 mg thio-TEPA, retained for 30 min immediately after resection of superficial (O A, CIS) tumors. Both cytotoxic agents were found to significantly reduce the incidence of recurrent tumors within the 3- to 6-month period of evaluation.

Other agents

Bleomycin. Bracken et al. [4] instilled bleomycin into the bladders of 26 patients with residual stage O–A tumors. A 3-week interval following staging endoscopy, an optimal dose of 60 U in 30 cm^3 volume, weekly instillations for 8 weeks, and a 2-h contact time are the critical details of this study. Systemic absorption was detected in only three of 23 patients at well below therapeutic or potentially toxic levels. There were no *clinical* signs of local toxicity, although at cystoscopy intense cystitis was noted in four of seven patients in whom the drug destroyed lesions. A complete response was seen in 27% but not in any patient with a large tumor burden.

A preliminary report [27] of low-order (13% CR) activity with intravesical cisplatinum awaits wider experience in this country, although it is currently being included in EORTC phase III trials [36].

Bacillus Calmett-Guerin (BCG). An attenuated bovine mycobacterium, BCG has been carefully studied in this country with exciting preliminary results. Following the original uncontrolled prophylaxis studies of Morales et al. [28, 29], other investigators initiated prospective randomized protocols to verify the activity of intravesical BCG.

Herr et al. recently updated [18] their results in 69 patients with multiple recurrent superficial bladder cancer randomized to endoscopic surgery with or without BCG therapy. BCG (Pasteur strain) was administered weekly for 6 weeks, both intravesically and percutaneously, starting 2 weeks after transurethral resection of all visible tumors. A statistically significant decrease in the tumor recurrence rate and in the number of patients exhibiting progressive disease requiring cystectomy was noted in the BCG group. Of 47 patients with positive pretreatment cytology, only two of 21 control patients converted to negative, as against 20 of 26 BCG-treated patients.

Lamm et al. [25] initiated a similar prophylactic BCG study and likewise recorded statistically significant results: a 50% recurrence rate in control patients, as against 21% in BCG patients followed for up to 4 years.

The primary activity of intravesical BCG against superficial bladder cancer has very recently been demonstrated by Morales et al. [30]. Twenty-three patients received 120 mg BCG instilled each week for 6 weeks. Complete ablation of

residual tumor was achieved in 14 patients (61%) and maintained throughout the period of observation (mean follow-up 27 months).

Toxicity with BCG therapy has been generally mild. Almost invariably mild transient frequency and dysuria result, with occasional hematuria and rate low-grade fever and malaise. Severe toxicity (28%) was seen with the extended BCG (Tice strain) treatment course of Brosman [6], and included chills and fever, severe lower tract voiding symptoms, abnormal liver function tests, and pulmonary infiltrate. Four of his patients required hospitalization. Whether these more severe symptoms relate to the specific strain of BCG, the duration of the treatment course, or other factors remains to be determined.

Current prophylactic BCG studies in this country have focused in two pertinent issues. Lamm et al. are evaluating the impact of the percutaneous BCG component, while Herr et al. have dropped this inoculation and are studying the value of maintenance therapy. Controlled trials comparing BCG with other intravesical agents are being formulated.

Carcinoma in situ

Intravesical trials in carcinoma in situ have been a natural development of current treatment recommendations for this condition, which have ranged from observation to immediate cystectomy. Active intravesical agents to date would include thio-TEPA, doxorubicin, and BCG. The necessity of maintenance therapy has been suggested for patients treated with doxorubicin [22]. Results of similar long-term studies with other agents are pending.

The future

Current new directions of study include noncytotoxic intravesical agents (e.g., interferon [21, 33]) and new routes of administration (e.g., oral methotrexate [17], pyridoxine [36], and retinoic acid derivatives [38]).

Several effective intravesical agents with manageable toxicity are now available to the clinician for consideration in the treatment strategy for superficial bladder cancer. Refinements of dose, concentration, volume, contact time, and schedule of instillations will follow from further clinical experience. Phase-III studies of these agents will focus not only on activity and toxicity but on economic issues as well. Other critical questions include the need for maintenance therapy, the relation of primary and prophylactic activity to tumor grade, and the potential for long-term toxicity.

References

1. Abrams PH, Choa RG, Gaches CGC, Ashken MH, Green NA (1981) A controlled trial of single-dose intravesical Adriamycin in superficial bladder tumours. Br J Urol 53: 585
2. Asahi T, Matsumura Y, Tanahashi T, et al. (1980) The effects of intravesical instillation of thiotepa on the recurrence rate of bladder tumors. Acta Med Okayama 34: 43
3. Banks MD, Pontes JE, Izbicki RM, Pierce JM Jr (1977) Topical instillation of doxorubicin hydrochloride in the treatment of recurring superficial transitional cell carcinoma of the bladder. J Urol 118: 757
4. Bracken RB, Johnson DE, Rodriquez L, Samuels ML, Ayala A (1977) Treatment of multiple superficial tumors of bladder with intravesical bleomycin. Urology 9: 161
5. Bracken RB, Johnson DE, von Eschenbach AC et al. (1980) Role of intravesical mitomycin C in management of superficial bladder tumors. Urology 16: 11
6. Brosman SA (1982) Experience with Bacillus Calmette-Guerin in patients with superficial bladder carcinoma. J Urol 128: 27
7. Burnand KG, Boyd PJR, Mayo ME, Shuttleworth KED, Lloyd-Davies RW (1976) Single-dose intravesical thiotepa as an adjuvant to cystodiathermy in the treatment of transitional cell bladder carcinoma. Br J Urol 48: 55
8. Byar D, Blackard C, and The Veterans Administration Cooperative Urological Research Group (1977) Comparisons of placebo pyridoxine and topical thiotepa in preventing recurrence of stage I Bladder cancer. Urology 10: 556
9. Camuzzi F, Bondus M, Lockhart J, Politano V (1980) Mitomycin C in the treatment of superficial bladder cancer. Proc Am Urol Assoc Abstract 120
10. DeFuria MD, Bracken RB, Johnson DE, et al. (1980) Phase I-II study of Mitomycin C topical therapy for low-grade, low-stage transitional cell carcinoma of the bladder: an interim report. Cancer Treat Rep 64: 225
11. Drew JE, Marshall VF (1968) The effects of topical thiotepa on the recurrence rate of superficial bladder cancers. J Urol 99: 740
12. Edsmyr F, Berlin T, Boman J, et al. (1980) Intravescial therapy with Adriamycin in patients with superficial bladder tumors. Eur Urol 6: 132
13. England HR, Flynn JT, Paris AMI, Blandy JP (1981) Early multiple dose adjuvant thiotepa in the control of multiple and rapid T_1 tumor neogenesis. Br J Urol 53: 588
14. Esquivel EL Jr, Mackenzie AR, Whitmore WF Jr (1965) Treatment of bladder tumors by instillation of thiotepa, actinomycin D or 5-fluorouracil. Invest Urol 2: 381
15. Garnick MB, Schade D, Israel M, Richie JP (1982) Clinical pharmacologic evaluation of intravesical Adriamycin for recurrent superficial bladder carcinoma. Proc Am Urol Assoc Abstract 445
16. Gavrell GJ, Lewis RW, Meehan WL, Leblanc GA (1978) Intravesical thiotepa in the immediate post-operative period in patients with recurrent transitional cell carcinoma of the bladder. J Urol 120: 410
17. Hall RR, Herring DW, Gibb I, Heath AB (1981) Prophylactic oral methotrexate therapy for multiple superficial bladder carcinoma. Br J Urol 53: 582
18. Herr HW, Pinsky CM, Whitmore WF Jr, Oettgen HF, Melamed MR (1983) Effect of intravesical Bacillus Calmette-Guerin (BCG) on carcinoma in situ of the bladder. Cancer 51: 1323
19. Hollister D, Coleman M (1980) Hematologic effects of intravesical thiotepa therapy for carcinoma of the bladder. J Urol 125: 307
20. Homonnai TZ, Paz G, Servadio C (1982) Sterilization following instillation of thiotepa into the urinary bladder. Br J Urol 54: 60
21. Ikic D, Maricic Z, Oresic V, et al. (1981) Application of human leucocyte interferon in patients with urinary bladder papillomatosis, treast cancer, and melanoma. Lancet I: 1022
22. Jakse G, Marburger H (1982) Adriamycin therapy for carcinoma in situ of the urinary bladder. Proc Am Urol Assoc Abstract 446
23. Jones HC, Swinney J (1961) Thiotepa in the treatment of tumours of the bladder. Lancet II: 615
24. Koontz WW Jr, Prout GR Jr, Smith W, Frable WJ, Minnis JE (1981) The use of intravesical thiotepa in the management of non invasive carcinoma of the bladder. J Urol 125: 307
25. Lamm DL, Thor DE, Winters WD, Stogdill VD, Radwin HM (1981) BCG immunotherapy of bladder cancer. Cancer 48: 82
26. Mishina T, Oda K, Murata S, et al. (1975) Mitomycin C bladder instillation therapy for bladder tumors. J Urol 114: 217

27. Mobley WC, Loening SA, Narayana AS, Culp DA (1982) The use of intravesical cisplatinum and mitomycin C for recurrent transitional cell carcinoma of the bladder refractory to intravesical thio-tepa. Proc Am Urol Assoc Abstract 495
28. Morales A, Ersil A (1979) Prophylaxis of recurrent bladder cancer with bacillus Calmette-Guerin: In: Johnson DE, Samuels ML (eds), Cancer of the genitourinary tract. Raven Press, New York, pp 121–132
29. Morales A, Eidinger D, Bruce AW (1976) Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 116: 180
30. Morales A, Pang ADS, Ottenhof PC (1982) Treatment of residual noninfiltrating bladder cancer with Bacillus Calmette-Guerin (BCG). Proc Am Urol Assoc Abstract 587
31. Nieh PT, Daly JJ, Heaney JA, Heney NM, Prout GR Jr (1978) The effect of intravesical thio-tepa on normal and tumor urothelium. J Urol 119: 59
32. Nissenkorn I (1981) Side effects associated with intravesical mitomycin C. J Urol 126: 596
33. Northern California Oncology Group: Protocol 4B-82-1
34. Oravisto KJ (1972) Optimal intravesical dosage of thiotepa in the prophylaxis of recurrent bladder papillomatosis. Scand J Urol Nephrol 6: 26
35. Osaki Y (1977) Bladder instillation of Adriamycin in the treatment of bladder tumors. 1: Clinical results. Jpn J Urol 68: 934
36. Pavone-Macaluso M, Ingargiola GB (1980) Local chemotherapy in bladder cancer treatment. Oncology [Suppl 1] 37: 71
37. Prout GR Jr, Griffin PP, Nocks BN, DeFuria MD, Daly JJ (1982a) Intravesical therapy of low-stage bladder carcinoma with mitomycin C: comparison of results in untreated and previously treated patients. J Urol 127: 1096
38. Prout GR Jr, Koontz WW Jr, Cutler S, et al. (1982a) A chemopreventive trial of cis-retinoic acid in patients with recurrent bladder carcinoma. Proc Am Urol Assoc Abstract 96
39. Smith PH (1981) Chemotherapy of bladder cancer: a review. Cancer Treat Rep [Suppl 1] 65: 165
40. Veenema RJ, Dean AL Jr, Roberts M, et al. (1962) Bladder carcinoma treated by direct instillation of thio-tepa. J Urol 88: 60
41. Veenema RJ, Dean AL Jr, Uson AC, Roberts M, Longo F (1969) Thiotepa bladder instillations: therapy and prophylaxis for superficial bladder tumors. J Urol 101: 711
42. Veenema RJ, Romas NA, and Fingerhut B (1974) Chemotherapy for bladder cancer. Urology 3: 135
43. Wescott JW (1966) The prophylactic use of thio-tepa in transitional cell carcinoma of the bladder. J Urol 96: 913
44. Zincke H, Utz DC, Taylor WF, Meyers RP, Leary FJ (1983) Influence of thiotepa and doxorubicin instillation at time of transurethral surgical treatment of bladder cancer on tumor recurrence: a prospective randomized, double-blind, controlled trial. J Urol 129: 505