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Diagnosis and treatment of bladder cancer

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The primary key to diagnosis of bladder cancer is cystoscopic examination of the bladder, followed by biopsy of suspicious lesions. Bimanual examination under anesthesia is also important for staging, and urinary cytology and intravenous urography provide valuable additional information. Surgical resection in the form of excisional transurethral biopsy is diagnostic, therapeutic and essential for accurate staging, and assessment of tumor grade is vital for determining prognosis and management strategies. Intravesical chemotherapy with Thiotepa, doxorubicin, mitomycin C or ethoglucid has been shown to reduce the incidence of short-term tumor recurrence by 17% but not long-term recurrence or rate of disease progression. Immunotherapy, as exemplified by *Bacillus Calmette-Guérin* (BCG), has achieved better results: long-term reduction in tumor recurrence, reduction in disease progression and prolongation of patient survival. Newer immunotherapies using interferon-α appear to produce response rates comparable to BCG but without the considerable toxicity of BCG. Further research with combination therapies and other immunotherapeutic agents should lead to improved treatment options in the future.

Key words: Bacillus Calmette-Guérin, bladder cancer, doxorubicin, ethoglucid, interferon-α2b, intravesical therapy, mitomycin C, Thiotepa

Introduction

In the USA an estimated 500 000 persons are living with bladder cancer, making it the fourth most prevalent noncutaneous malignancy. Three-quarters of patients present with superficial disease which is amenable to complete surgical resection, but following resection more than 75% of patients will have disease recurrence. In patients who survive 15 years, as many as 90% will have tumor recurrence. The number of new cases of bladder cancer continues to rise each year. In 1991 it was estimated that 50 200 persons were diagnosed with bladder cancer and 9500 died of the disease[1]. The high incidence, prevalence and recurrence rate of bladder cancer increase the need for effective treatment of this disease.

The most frequent age of onset of the disease is in the mid-sixties and men are affected three times as often as women. Transitional cell carcinoma accounts for over 90% of bladder malignancies, followed by squamous cell carcinoma (5%), adenocarcinoma (less than 2%) and rhabdomyosarcoma (less than 1%).

Etiology

Bladder cancer is one of the first malignancies demonstrated to result from exposure to chemical carcinogens. β-Naphthylamine, previously associated with aniline dyes and used as an antioxidant in the rubber industry, is one of several potent bladder carcinogens which have been identified and largely removed from the modern workplace, but epidemiologic studies show continued increased risk in a wide variety of occupations having exposure to gasoline, paints, oils, chromium and zinc.[2] Although industrial carcinogens are important, the number of persons exposed to these potent agents is small relative to the numbers exposed to the less potent carcinogen tobacco. It has been estimated that over 50% of the cases of bladder cancer in men and 25–33% of the cases in women are due to cigarette smoking. Evidence suggests that smokeless tobacco is also a bladder carcinogen, but passive smoke is yet to be implicated. Additional risks for bladder cancer include chronic infection and inflammation, phenacetin abuse, cyclophosphamide and pelvic irradiation. Even increased water consumption in some areas of the world is associated with an increased risk of bladder cancer, an observation which points out the futility of attempts to eliminate completely all risk factors for cancer. While viral oncogenes have been identified in transitional cell carcinoma as well as in a number of other cancers, such material is thought

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to be an intrinsic component of the vertebrate genome. Viral oncogenes are apparently an integral part of the process of malignant transformation, but there is currently no evidence that the viral infection *per se* results in bladder cancer.

Clinical features

Eighty per cent or more of patients with bladder cancer present with hematuria. Bleeding is typically intermittent, painless and easily visualized, but microscopic hematuria is also common. Microhematuria, which can be tested daily for 2 weeks by patients themselves using test tape, is proving to be a remarkably sensitive screen for bladder cancer. The intermittent nature of bleeding should be stressed, since patients and physicians alike can be mistakenly reassured when hematuria resolves. The patient who presents with advanced disease and a history of a previous episode of hematuria which was not fully evaluated is a tragedy which is repeated all too often.

Symptoms of vesical irritability, including frequency, urgency and dysuria, occur in as many as 33% of patients. Such symptoms may mimic cystitis and prostatitis. Tumors of higher grade, including carcinoma *in situ*, have an increased propensity to cause irritative symptoms. Fortunately, higher grade tumors, especially carcinoma *in situ*, are more likely to have a diagnostic urinary cytology. Urinary cytology, therefore, is a useful screen for bladder cancer in these patients.

Symptoms of advanced disease, including weight loss, abdominal mass, suprapubic or flank pain and lymphedema, are rarely observed today.

Diagnosis

Cystoscopic examination of the bladder continues to be the primary key to diagnosis, since urinary cytology and imaging studies have high false negative rates. Flexible cystoscopy can be accomplished without anesthesia in the majority of patients, but rigid cystoscopy provides a clearer view of the bladder. It is axiomatic that the entire surface of the bladder should be carefully and closely viewed, and a 120° lens should be used if the anterior bladder neck is not visualized with the 70° lens. A high degree of suspicion is appropriate if raised, roughened or reddened areas are seen, and these are best biopsied with cupped forceps. Often one or two biopsies can be done in the office, but more extensive biopsies and initial tumor resection are best done under anesthesia so that completeness is not compromised by concern for patient discomfort. Bimanual examination under anesthesia is also an integral part of clinical staging, as even small superficial-appearing tumors can be associated, on rare occasions, with an unsuspected, non-visualized, but palpable mass.

Even careful and expert cystoscopic examination may fail to diagnose bladder cancer, as carcinoma *in situ* may be entirely normal in appearance. Most bladder tumors are more red in color than surrounding urothelium and can be seen from a distance. Tumors that are exactly the same shade as the rest of the bladder can be easily missed unless the bladder wall is inspected from close range. Fortunately, urinary cytology is almost invariably positive in patients with carcinoma *in situ* since tumor cells are highly anaplastic, have defective intercellular adherence and readily slough off into the urine. Indeed, in some cases the diagnosis of carcinoma *in situ* is more easily made with urinary cytology than bladder biopsy, since biopsy may only show the denuded, inflamed bladder wall.[3]

Methylene blue has been used to stain transitional cell carcinoma and facilitate visualization and selection of biopsy sites. This technique is most useful in patients who have a positive cytology and no visible tumor. A solution of 0.2% methylene blue is placed in the bladder for 10 min prior to cystoscopy. Transitional cell carcinoma and areas of inflammation can be identified by blue staining.

Random bladder biopsy helps to determine the prognosis and select treatment for patients with bladder cancer. Biopsies are taken of the tumor margins, visibly suspicious areas, normal appearing urothelium at multiple preselected sites such as the lateral walls, dome, posterior wall, trigone and bladder neck, and, importantly, the prostatic urethra. Atypia or carcinoma *in situ* are poor prognostic signs[4] and up to 40% of patients undergoing cystoprostatectomy are found to have transitional cell carcinoma in the prostatic urethra. The latter is of particular importance with the advent of orthotopic bladder substitution procedures where recurrence of tumor in the urethra can be devastating.

In addition to urinary cytology, which is highly variable in accuracy at different institutions, some have used flow cytometry, quantitative fluorescence image analysis (QFIA), monoclonal antibody immunocytology, quantitation of nuclear

roundness and nuclear/cytoplasmic ratio, and fibrin degradation product (FDP) analysis to aid the diagnosis of bladder cancer. In my experience FDP has been more accurate than flow or QFIA. Recently immunocytology has been reported to have a 90% sensitivity compared with 70% for standard cytology and less than 50% for flow cytometry.[5] Currently, however, these additional diagnostic techniques are generally considered investigational and their place in routine clinical management remains to be defined.

Intravenous urography (IVP) remains the mainstay of radiographic evaluation in bladder cancer. The IVP provides efficient visualization of the upper urinary tract and is useful in the differential diagnosis of hematuria. While upper tract tumors occur in only 2–3% of patients with bladder cancer, carcinoma *in situ* occurs much more frequently and a baseline IVP or retrograde pyelogram is needed to demonstrate upper tract anatomy. For superficial tumors not invading the detrusor muscle additional imaging studies such as cystograms, pelvic computed tomography, magnetic resonance imaging, ultrasonography and bone scans are neither necessary nor cost effective.

Surgery

Excisional transurethral biopsy (resection) is diagnostic, therapeutic and essential for accurate staging. Transurethral surgery requires extensive experience and endoscopic training as well as considerable manual dexterity. I prefer to begin resection in relatively safe areas, avoiding the dome and lateral walls overlying the obturator nerve until all other tumors have been removed so that the procedure can be terminated quickly if bladder perforation occurs. Cautery current should be minimized to avoid charring of the specimen, but sufficient cutting current should be used to permit smooth, easy cutting. Muscle should be included in the specimen to permit accurate staging and care is taken to avoid distension of the bladder so that these specimens can be taken without perforating a thinned out bladder. Areas of carcinoma *in situ* are fulgurated and the roller electrode is used to fulgurate the tumor base and margins of resection. After resection of all visible tumors the 70° lens is reinserted to confirm resection of all tumors. This post-resection cystoscopic examination is important for even the most experienced surgeon.

Pathology and staging

Pathologic review should include information of prognostic importance to clinical management. Tumor grade is critically important. Grade I tumors rarely progress to muscle invasion, with only 2% of grade I stage T_a tumors and 7% of grade I stage T_1 tumors progressing. In contrast, progression with grade III tumors is common: 25% for grade III stage T_a and 48% for grade III stage T_1.[4] Similarly, tumor stage must be defined. Thirty percent of tumors with lamina propria invasion, stage T_1, will progress in less than 4 years. If muscle invasion is present, aggressive treatment rather than intravesical therapy is required. Stage T_2 tumors, invading less than half way through the detrusor muscle, stage T_{3a} tumors, invading into the second half of the detrusor muscle, and stage T_{3b} tumors, extending into perivesical fat, are all best treated with radical cystectomy. The advent of continent diversion for women and nerve-sparing cystectomy with orthotopic bladder reconstruction in men has greatly increased patient acceptance of radical cystectomy.

Indications for intravesical therapy

Not all patients with superficial bladder cancer require intravesical therapy. Patients with a solitary low-grade stage T_a tumor are at low risk of recurrence and progression and can be spared the expense and morbidity of intravesical therapy. Those at increased risk of tumor progression are clearly candidates for adjunctive therapy and those at risk for recurrence can benefit from intravesical therapy as well. Clear indications for intravesical therapy, in my opinion, include multiple primary tumors, tumor recurrence, grade III tumor, stage T_1 tumor, positive post-resection urinary cytology and dysplasia or carcinoma *in situ* on random biopsy.

The goals of intravesical therapy are the prevention or postponement of tumor recurrence, eradication of residual unresectable papillary transitional cell carcinoma or carcinoma *in situ*, prevention of tumor progression, reduction of the need for radical cystectomy, and maintenance and prolongation of good quality life. While prevention of tumor recurrence is a significant achievement, prevention of tumor progression is clearly the important goal.

Intravesical chemotherapy

Effective intravesical chemotherapy dates back to 1955 when Thiotepa was first instilled in the bladder in patients with superficial bladder cancer. Since that time, controlled studies have demonstrated that the four commonly used intravesical cytotoxic chemotherapies are effective in the treatment of residual tumor and the short-term prevention of tumor recurrence. The four most commonly used and effective intravesical chemotherapies are: Thiotepa, doxorubicin, mitomycin C (MMC) and ethoglucid. Published response rates in 1582 patients with residual papillary transitional cell carcinoma show average complete response rates of 29% for Thiotepa, 38% for doxorubicin, 47% for MMC and 55% for ethoglucid.[6] While these data suggest that ethoglucid and MMC may be more effective than Thiotepa, prospective controlled studies have failed to confirm the superiority of newer chemotherapies over Thiotepa. Twenty randomized prospective studies have compared intravesical chemotherapy with surgery alone (Table 1).[7] Six of 10 Thiotepa studies showed a statistically significant advantage for intravesical Thiotepa.[8] Reduction in tumor recurrence averaged 17%. Two of four doxorubicin studies were statistically significant and average benefit of treatment was an 18% reduction in tumor recurrence. Five controlled MMC trials revealed an average reduction in tumor recurrence of only 15% and only two studies achieved statistical significance.[8] Only one controlled ethoglucid trial has been done, but statistically significant reduction in recurrence of 31% was achieved. In the combined experience with 20 controlled chemotherapy trials, 11 were statistically significant and overall reduction of tumor recurrence in 2799 patients averaged 17%.

More than a dozen studies comparing one

Table 1. The 20 published chemotherapy trials that have compared adjuvant intravesical therapy with transurethral resection alone. For these references in full please consult Reference 7, given at the end of this paper

First author	No. of studies	Control recurrence (%)	Treatment recurrence (%)	Benefit (%)	*p*
Thiotepa					
Burnand 1976	51	97	58	39	0.001
Byar 1977	88	60	47	3	0.016
Nooks 1979	42	64	65	−1	NS
Asahi 1980	106	37	37	0	NS
Sohulman 1980	144	52	49	3	NS
Macaluso 1980	94	60	23	37	S
Koontz 1981	93	66	40	26	0.02
Zincke 1983	58	71	30	41	0.002
Prout 1983	90	76	64	12	0.05
MRC 1985	243	32	37	−5	NS
Total	1009	62	45	17% Adv	
Doxorubicin					
Niijima 1983	288	45	30	15	0.05
Zincke 1983	59	71	32	39	0.01
Kurth 1985	155	48	35	13	NS
Rübben 1988	220	61	56	5	NS
Total	722	56	38	18% Adv	
MMC					
Huland 1983	58	40	7	33	0.01
Niijima 1983	278	46	37	9	NS
Kim 1988	43	68	67	1	NS
Tolly 1988	397	65	42	23	0.001
Rübben 1990	83	42	35	7	NS
Totals	859	52	37	15% Adv	
Ethoglucid					
Kurth 1985	209	59	28	31	0.0004
Overall total	2799	58	41	17% Adv	

intravesical chemotherapy with another have failed to confirm that any of the newer chemotherapies are significantly better.[8] Extensive data now confirm that intravesical chemotherapy reduces the rate of short-term tumor recurrence, by a modest 17%, but the long-term rate of tumor recurrence and, more importantly, the rate of disease progression unfortunately fail to be reduced, as illustrated in Table 2. With over 1400 patients enroled in controlled studies, evidence fails to support the conclusion that intravesical chemotherapy reduces the rate of tumor progression. One approach to improve the benefits of intravesical therapy has been to keep patients on maintenance regimens. Recently, reports by both Flamm[11] and Huland *et al.*[12] demonstrate that maintenance doxorubicin or MMC offer no benefit over shorter courses. Indeed, the observation that very early short-course chemotherapy provides the highest relative benefit has been suggested. With Thiotepa, the two studies showing the greatest advantage (Burnand and Zincke[7]), and indeed the only study (Burnand[7]) to show a statistically significant advantage of Thiotepa at the $p < 0.001$ level used early post-operative treatment.

Immunotherapy

It is a mistake to lump chemotherapy together with immunotherapy since the mechanisms of action, the principles of treatment and the potential benefits of therapy are distinctly different. The commonly used intravesical chemotherapies, with the exception of the intercalating agent doxorubicin, are alkylating agents and have a similar mechanism of action. Immunotherapy, as exemplified by the first successful immunotherapy of bladder cancer, *Bacillus Calmette-Guérin* (BCG), stimulates immune defences. While cytotoxic chemotherapy is effective only against extant malignancy, immunotherapy has the potential of inducing specific immunity to tumor, making the prevention of tumors that have not yet developed feasible. Currently BCG is the only immunotherapeutic agent that is specifically approved for the treatment of bladder carcinoma *in situ* in the USA, although interferon (IFN)-α is commercially available and as illustrated by the reports in this issue, highly effective.

BCG immunotherapy

Following the demonstration in the early 1970s that BCG could cause regression of cutaneous malignancies, numerous investigators independently evaluated BCG immunotherapy in bladder cancer. Morales was the first to report clinical success in 1976, when he observed a 12-fold reduction in tumor recurrences in patients given a 6 week course of intravesical and percutaneous BCG.[13] BCG immunotherapy has subsequently been confirmed by investigators around the world to be highly effective in the reduction of tumor recurrence, the treatment of residual papillary transitional cell carcinoma and, most importantly, the treatment of carcinoma *in situ*. Response rates in the treatment of residual papillary disease average 55%. In the treatment of carcinoma *in situ*, with 663 patients treated in 15 studies around the world, the average complete response rate is 73%, higher than with any intravesical agent.

In the prevention of tumor recurrence, as shown in Table 3, the relative benefit of BCG is 45% in

Table 2. The results of seven randomized studies with 1423 patients treated with the most common intravesical drugs, Thiotepa, MMC, and doxorubicin. No study achieved statistical significance and progression averaged 6.6% with treatment and 7.2% with no treatment. For these references in full please consult Reference 7, given at the end of this paper

	Treatment no.	Progression	Control	Progression
Green 1984	Thiotepa 25	1 (4%)	31	6 (19%)
Prout 1983	Thiotepa 45	6 (13.3%)	45	4 (8.9%)
MRC 1985	Thiotepa 244	7 (2.8%)	123	2 (1.6%)
Huland 1983	MMC 28	1 (4%)	30	6 (20%)
Tolly (MRC) 1988	MMC 267	6 (2.2%)	130	2 (1.5%)
Rübben 1988	Doxorubicin 138	19 (14%)	82	10 (12%)
Kurth 1989	Doxorubicin 165	20 (12%)	70	7 (10%)
Total	912	60 (6.6%)	511	37 (7.2%)

367 patients, and four of five controlled studies are statistically significant at $p < 0.001$.[6] Direct prospective randomized comparisons of BCG with intravesical chemotherapy have found it to be significantly superior to Thiotepa, doxorubicin and MMC in the prevention of tumor recurrence.

In view of the consistent increased benefit of immunotherapy with BCG compared to chemotherapy, it is surprising that only one of four controlled comparisons have found BCG to be significantly better than MMC. It is equally surprising that only two of five studies found MMC to be superior to surgery alone. While one can speculate about the use of suboptimal treatment doses and schedules, these observations can be explained by statistical considerations. If the superiority of BCG over mitomycin is equal to the average superiority of mitomycin over control, i.e. 15%, then 338 patients would have to be evaluable for $p < 0.05$ (Epistat). Even with a study of that magnitude, only four of five studies would achieve statistical significance. Since no study that large has been published, it is not surprising that only one of four studies found BCG to be significantly superior to mitomycin. Fortunately, a study of adequate size is underway in the Southwest Oncology Group and the definitive answer should be available in 1993.

When intravesical chemotherapy is used prophylactically, tumor recurrence is delayed, but by 5 years the percentage of patients who have recurrence is the same as in patients who have not received this therapy.[8] With BCG immunotherapy, however, benefits appear to be long term. For example, in our Southwest Oncology Group study comparing BCG with doxorubicin in patients with rapidly recurring transitional cell carcinoma, only 17% of patients were estimated (Kaplan Meier) to be tumor free at 5 years compared with 37% of BCG treated patients. In patients with carcinoma *in situ*, the difference was even more pronounced, 18 versus 45% ($p < 0.0001$).[14]

Tumor progression

While chemotherapy has failed to reduce tumor progression, evidence suggests that immunotherapy with BCG does in fact reduce tumor progression. In our experience with 90 nonrandomized patients, progression to muscle invasion was reduced from 8% in controls to 3% with BCG therapy. This difference was not statistically significant, but the reduction in invasion of lamina propria from 23 to 6% was significant ($p < 0.05$). In randomized studies, Herr *et al.*[15] observed a reduction in muscle invasion from 46 to 28% with BCG treatment ($p < 0.01$) and Pagano *et al.*[16] observed a reduction from 18 to 4% ($p < 0.001$). The need for cystectomy was similarly significantly reduced in Herr's study, and despite the more frequent and earlier use of cystectomy, mortality was significantly reduced in the BCG group from 32 to 14%.

BCG complications

Although 95% of patients tolerate BCG without significant toxicity, serious and even fatal reactions can occur. Septic reactions, characterized by fever, hypotension, disseminated intravascular coagulopathy and multiorgan failure, have been temporally associated with BCG administration. Such reactions are typically associated with traumatic catheterization or intravenous absorption of BCG. Recent evidence suggests that hypersensitivity is a

Table 3. The five published randomized prospectively controlled comparisons of surgery alone and surgery plus BCG immunotherapy. All but one of these studies reported a highly significant advantage for patients receiving BCG. In contrast to chemotherapy, where the relative benefit ranges from 15 to 18% and is short term, the benefit of BCG averages 40-45% and appears to last at least 5 years. For these references in full please consult Reference 7, given at the end of this paper

	N	Control recurrence (%)	BCG recurrence (%)	Benefit (%)	*p*
Lamm 1985	57	52	20	32	<0.001
Herr 1985	86	95	42	53	<0.001
Herr 1986 (CIS)	49	100	35	65	<0.001
Pagano 1989	98	83	15	68	<0.001
Rübben 1990	77	42	35	7	NS
Total (no CIS)	318	68	28	40	<0.000
Total (without CIS)	367	74	29	45	<0.000

significant component of this toxicity, and current recommendations for treatment are isoniazid 300 mg, rifampin 600 mg and prednisolone 40 mg daily. Unpublished animal studies from my laboratory confirm that cycloserine can also improve survival over isoniazid and rifampin. Treatment with prednisolone alone was ineffective.

IFN-α2b

The remarkable efficacy of immunotherapy with BCG has highlighted the potential of immunotherapy in the treatment of superficial bladder cancer and raises the question: can alternative immunotherapies produce the benefits of BCG without the toxicity? Various immunotherapeutic agents are now being evaluated around the world.

Considerable evidence suggests that IFN-α2b (Intron A, Schering-Plough) has efficacy in the treatment of transitional cell carcinoma. In a phase I–II trial, Torti *et al.* evaluated IFN-α2b in heavily pretreated patients with papillary and *in situ* transitional cell carcinoma.[17] In patients with papillary transitional cell carcinoma, complete response was observed in four of 16 patients, three of whom had previously failed to respond to intravesical chemotherapy. As expected with immunotherapeutic agents, response in carcinoma *in situ* was higher. Nine of 19 carcinoma *in situ* patients (47%) had a complete response, although three of these patients had subsequent grade I papillary transitional cell carcinoma; patients with prior chemotherapy had a complete response rate that was not significantly different from the response rate in those who had not had prior chemotherapy. The response rates to interferon in the treatment of carcinoma *in situ* compare very favorably to those with chemotherapy and even BCG. The dosage of IFN-α2b in this study ranged from 50 to 1000 MU given intravesically weekly for 8 weeks. Complete responses at the lower doses (50–100 MU) occurred as frequently as responses at doses of 400–1000 MU. Five of 10 patients with complete response remained disease free at 18+ to 37+ months. Importantly, no serious toxicity was observed in this study. No patient had hematuria, dysuria or myelosuppression. Only 15 of 55 patients (27%) had mild flu-like symptoms. The maximum tolerated dose was not reached at 1000 MU. The dose response observed in this study confirms that, unlike chemotherapy, the maximum tolerated dose of a biologically active drug is not necessarily the most effective dose.

In a subsequent phase III trial, Glashan and coinvestigators randomized 87 patients with carcinoma *in situ* to receive 10 or 100 MU of IFN-α2b weekly for 12 weeks followed by monthly instillations to 1 year.[18] Two of 38 patients (5%) that received low-dose interferon had a complete response, while 20 of 47 patients (43%) that received high-dose interferon had a complete response ($p < 0.0001$). In the low-dose group, an additional 12 patients (32%) had biopsy evidence of complete resolution of carcinoma *in situ*, but had residual positive urinary cytology. In the high-dose group, an additional nine patients had complete response by biopsy, but not cytology. In the low-dose group, disease progression was observed in 37% of patients compared with only 13% of those in the high-dose group. The duration of complete responses in this study ranged from 6 months to now over 5 years, with two patients from a group of nine BCG failures showing a complete response to 100 MU Intron A lasting for 12 months and over 5 years, respectively.

Systematic absorption of interferon in this study was not observed. As with all previous studies, no local toxicity occurred and flu-like symptoms were uncommon, occurring in only 8% of the low-dose and 17% of the high-dose subjects.

From the available clinical and laboratory studies it appears that IFN-α has definite antitumor activity. Phase II studies have demonstrated efficacy in the treatment of papillary and *in situ* transitional cell carcinoma. Preliminary studies have suggested efficacy in reduction of tumor recurrence. Most importantly, a multicenter randomized prospective phase III study has demonstrated that high-dose IFN-α is superior to low-dose and can be given without evidence of toxicity.

Alternate immunotherapies

Keyhole limpet hemocyanin (KLH)

Considerable laboratory and clinical evidence now suggests that the highly antigenic respiratory pigment (hemolymph) of the mollusc *Megathuria crenulata* has significant antitumor activity. Unpublished animal studies from my laboratory show that KLH can be as effective as BCG and the addition of IFN-α can further increase efficacy. Studies in Europe have suggested that intravesical and percutaneous KLH results in bladder tumor recurrence rates which are less than that observed with MMC[9] and equal to that observed with ethoglucid.[10]

Interleukin-2 (IL-2)

Originally termed T cell growth factor, IL-2 is produced by helper T lymphocytes and serves to stimulate lymphocyte proliferation. Intralesional IL-2 was reported by Pizza *et al.* to result in complete tumor regression in three of six patients receiving 4000 U of IL-2.[19] Huland and Huland have similarly observed complete response in one of four patients given continuous infusion intravesical IL-1, suggesting activity of IL-2 in bladder cancer.[20]

Other immune active agents with a suggestion of activity in bladder cancer include maltose tetrapalmitate, OK-432, a lypophilized attenuated streptococcus vaccine, and the IFN inducers poly-(I)·poly(C) and Bropirimine.

Conclusions

Intravesical chemotherapy results in tumor regression in 25–50% of patients with papillary and *in situ* transitional cell carcinoma of the bladder. Used prophylactically, chemotherapy reduces short-term tumor recurrence by an average of 17%, but does not appear to reduce long-term recurrence, disease progression or mortality. Efforts are underway to improve intravesical chemotherapy and multiple approaches not feasible with systematic chemotherapy are possible.

Immunotherapy, as exemplified by BCG, has a mechanism of action which is different from that of classic cytotoxic chemotherapy. BCG results in regression of 50–80% of papillary and *in situ* carcinomas, and reduces tumor recurrence by as much as 50%. The benefits of BCG immunotherapy appear to be long term in some patients, and controlled studies suggest that tumor progression and even mortality can be reduced. Enthusiasm for widespread use of BCG is tempered by concern regarding significant toxicity. Alternative immunotherapies have the prospect of being highly effective as well as less toxic. Although few alternative immunotherapies are commercially available in the USA at this time, research is under way to develop these agents. IFN-α2b is one agent which has demonstrated antitumor activity in papillary (25% complete response) and *in situ* (47% complete response) carcinoma. Multicenter controlled phase II evaluation has confirmed the efficacy of IFN-α2b in the treatment of carcinoma *in situ*. Further research and possibly the use of combination immunotherapies should result in significantly improved treatment options in the future.

Summary of the principles of treatment for bladder cancer

Currently available therapies for the treatment of bladder carcinoma fall into three main categories:

(1) Surgery
(2) Radiotherapy
(3) Chemotherapy

The effectiveness of these approaches varies widely and current opinion on their usefulness us summarized below.

Surgery

Options for treatment include, as first line therapy, the use of surgical procedures to remove carcinomatous tissue. These procedures include:

(1) Endoscopic resection and fulguration for the treatment of superficial lesions as an initial diagnostic as well as therapeutic step.
(2) Segmental bladder resection for the removal of large single lesions located in either the dome of the bladder or the lateral wall, particularly in patients in whom total cystectomy is considered to carry too high a risk factor.
(3) Cystectomy in patients who have no metastases outside the pelvic area and who have a good life expectancy but in whom the tumor invades the detrusor muscle or has failed less radical approaches and is likely to progress.

Radiotherapy

Sole use of radiotherapy as a definitive, front-line therapy, is rarely indicated due to both low response and survival rates, although such treatment may be used as a means of controlling bleeding and pain in both metastatic or high grade (III, IV) tumors. Even when used as an adjuvant in conjunction with radical cystectomy, radiation therapy has not been shown to result in improved survival. Preliminary studies, combining chemotherapeutic drugs such as cisplatin or 5-fluorouracil with radiotherapy, are encouraging, but have not yet demonstrated clear superiority over radiation alone.

Chemotherapy

A range of therapeutic agents has been used in the treatment of bladder carcinoma following tumor resection. Response rates of between 10 and 41% have been shown in the metastatic phase of such carcinomas using cisplatin, cyclophosphamide, doxorubicin, 5-fluorouracil, methotrexate and MMC. The best overall response rates derived from the use of a single agent are those seen with cisplatin, which is presently being used in combination therapy with vinblastine and methotrexate.

Chemotherapeutic drugs may also be used intravesically and such an approach has been adopted through instillation with doxorubicin, MMC and thiotepa. Recent studies suggest that intravesical immunotherapy offers advantages not seen with chemotherapy, including protection from tumor recurrence which persists for 5 years, or more, reduction in stage progression and reduction in cancer mortality. Immunotherapy with BCG has been most extensively studied. Recent trials suggest that the immunological agent IFN-α provides the benefits of immunotherapy with fewer side effects than BCG or chemotherapy.

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