Drugs 1997 Mar; 53 (3): 404-414
0012-6667/97/0003-0404/$11.00/0

Current Recommendations for the Management of Bladder Cancer

Drug Therapy

J. Alfred Witjes

Department of Urology, University Hospital Nijmegen, Nijmegen, The Netherlands

Contents

Summary

Superficial transitional cell carcinoma of the bladder is a heterogeneous group of tumours, and prediction of disease outcome in an individual patient is still impossible. In low-risk patients the initial treatment [transurethral resection (TUR)] should be followed by no or only one immediate intravesical instillation with a chemotherapeutic drug to prevent a recurrence due to tumour cell implantation during TUR. Drug efficacy has been clearly demonstrated and adverse effects are very limited. Intermediate-risk patients should receive a course of additional intravesical instillations to reduce the recurrence rate with few adverse effects. All drugs seem to be equally effective, but the long term effects remain a question. In high-risk patients intravesical immunotherapy (BCG) should be given. Although toxicity is more pronounced, it is usually mild and adverse effects disappear after cessation of therapy. BCG (maintenance) therapy seems to be able to improve progression and ultimately tumour-related survival. It is important to know the advantages and disadvantages (adverse effects) of these treatment modalities to be able to individualise treatment as much as possible. The choice is

difficult because several intravesical bladder cancer trials have not reached consensus on this.

For patients with non-metastasised invasive bladder tumours chemotherapy can be given before (neoadjuvant) or immediately after (adjuvant) surgery or radiotherapy. Both strategies have some advantages and disadvantages. For both, however, efficacy still needs to be proven, and results of ongoing trials are needed. For metastasised or recurrent urothelial cell carcinoma MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy remains the most effective treatment modality. Although initial response rates of between 40% and 70% can be achieved, most patients have a recurrence of their cancer. Moreover, toxicity of these drugs also is considerable and limiting. Leucopenia is responsible for the majority of grade III and IV toxicities and subsequent dose modifications. In case of toxic deaths, a leucopenic sepsis is usually the cause. Most other adverse effects are acceptable or can be treated.

Bladder cancer is the second most common malignancy of the urinary tract, and accounts for 2% of all malignancies. In 1993 52 300 cases were registered in the US, while the number who died of bladder cancer that year was 9900. In 1992 in the Netherlands a total of 3777 bladder tumours was registered, which accounted for 5.7% of all malignancies.[1] Bladder cancer is predominantly seen in the sixth and seventh decade of life. The male to female ratio is approximately 4 : 1. These epidemiological data, however, are changing due to changes in the smoking behaviour among men and women.[2]

About two-thirds of bladder tumours will present as superficial [pTa (papillary noninvasive carcinoma, limited to the bladder mucosa), pT1 (tumour not extending beyond the lamina propria of the bladder), carcinoma *in situ* (CIS; pre-invasive flat carcinoma)] transitional cell carcinomas (TCC).[3] The recurrence rate of these superficial tumours is high and depends on several factors. In our series of primary cases the 3-year risk of first recurrence ranged from 37% in low risk patients to 77% in high risk patients (overall nearly 55%). In a review of 6 historical series with long term follow up, the recurrence rates after 5, 10 and 15 years were 65%, 81% and 88%, respectively.[4] Most recurrences are found in the first years after transurethral resection (TUR)[5] and have the same stage and grade. These tumours can be true recurrences (regrowth after incomplete TUR or a result of implantation of tumour cells during TUR) and/or new occurrences. Prevention of implantation of the tumour is the rationale for immediate instillation of a chemotherapeutic drug.

The actuarial risk of disease progression in our series on bladder cancer patients was 10.2% after 3 years, with a 5-year relative survival rate of 86%.[3] This is in concordance with data from the literature.[6]

With these data it is possible to select prognostic factors, like tumour grade and especially stage, recurrence rate, multiplicity, size and localisation. With such factors, three risk groups can be constructed: low-risk patients, a minority, have a low chance of recurrence, and almost no progression. An example is a primary, small, solitary, well to moderately differentiated pTa tumour; intermediate-risk patients comprise the largest group, and consist of patients who develop a superficial recurrence without obvious progression; and a small group of patients have high-risk tumours with a high recurrence rate and a chance of progression despite maximal intravesical treatment. Patients with multiple recurrent pT1 grade 3 tumours and/or CIS belong to this last group.

Many other prognostic factors, like DNA ploidy, chromosomal abnormalities and marker chromosomes, have been described in the past few decades, but none is able to predict recurrence or progression in an individual patient.[7]

1. Initial Treatment

The cornerstone of the diagnosis of bladder cancer remains a TUR with or without mucosal biopsies. With this TUR specimen histology (> 90% TCC), tumour grade and stage can be determined. In case of a superficial bladder tumour a complete TUR with deep biopsies gives sufficient information to evaluate the need for additional treatment. These intravesical instillations can be used to delay or prevent tumour recurrences (prophylaxis). In the case, however, of an incomplete resection (e.g. CIS), or contraindications against surgery, instillations are used to eradicate tumour (treatment).

Advantages of the intravesical route of administration are limited systemic uptake of the drug with an optimal contact between the tumour or tissue at risk and the drug. Disadvantages are the local adverse effects in the bladder due to high local drug concentration and the need for transurethral manipulation. Instillations can be done with chemotherapeutic agents or immunotherapeutic agents. In low-risk patients the need for adjuvant treatment is low.[8] In the intermediate risk group intravesical instillations may be used to decrease the recurrence rate. In patients with high-risk tumours intravesical immunotherapy could be considered, although the higher efficacy comes at a cost of more adverse effects.

2. Additional Therapy of Superficial Bladder Cancer

2.1 Intravesical Chemotherapy

Because most chemotherapeutic drugs are cell cycle–specific, repeated instillations seem more effective than single instillations. Although weekly or monthly instillations might be very practical, they are probably not ideal from a molecular biological (cell cycle) point of view.

For chemotherapeutic drugs, a molecular weight of less than 200 and subsequent systemic absorption and toxicity are important. Local adverse effects, like drug-induced cystitis, are the main adverse effects, increasing with the number and frequency of instillations and with the dose.

2.1.1 Thiotepa

Thiotepa is relatively inexpensive and is not cell cyclespecific. It has a low molecular weight of 189, and thus absorption and systemic toxicity can occur. Usually 30 to 60mg is used, although 30mg in 30ml seems to be as effective as 60mg in 60 ml.[9] After 6 weekly instillations treatment is generally continued for 1 year with monthly instillations.

Toxicity is mainly due to systemic absorption (leucopenia and thrombocytopenia in approximately 10%) and 25% of patients have irritative bladder complaints.[10]

In 10 small series, thiotepa as definitive therapy for papillary bladder tumours has had a moderate success rate (complete responders) of approximately 38% (109 of 285).[11,12]

In a large randomised trial (n = 379), no advantage of thiotepa was reported using single immediate instillations after a complete TUR.[13] For other adjuvant treatment schedules Lamm[14] recently compared the recurrence rate of thiotepa (45%) to the recurrence rate in control groups (62%) in a series of 10 controlled studies with 1009 patients. The results depended on the follow-up period and in 5 of the 10 series failed to reach statistical significance, including the 3 largest series. Two other large series also failed to show a statistically significant advantage for thiotepa, in spite of a lower recurrence rate in the treated patients.[15,16] In 2 other controlled studies thiotepa was proven to be equally effective compared with doxorubicin.[17,18]

In summary, thiotepa is inexpensive, but its efficacy is questionable. Adverse effects such as myelosuppression and chemical cystitis are not frequent and usually mild.

2.1.2 Doxorubicin

Doxorubicin has a relatively high molecular weight of 580, and thus its absorption and systemic toxicity are extremely rare. The dose of doxorubicin ranges from 30 to 100mg in several instillation schedules. Its main adverse effect is chemical cystitis in 25% of patients.[10,19]

The average complete response rates of doxorubicin used as definitive treatment for papillary tumours was 38% (273 of 712), depending on the

dose used.[12] For CIS the reported success rate was 63% (77 of 122), but the numbers were small.

In his review, Lamm[14] found no significant advantage of doxorubicin (recurrence rate of 38 versus 56% in control patients) in the prophylactic setting. The Japanese Urological Cancer Research Group found a significant advantage for doxorubicin with regard to recurrences, but they found no advantage of a maintenance schedule over a course of intravesical instillations.[20,21]

In summary, in the treatment of bladder cancer patients, doxorubicin is a relatively safe drug with reversible chemical cystitis occurring in approximately 25% of the patients. The success rate of doxorubicin is slightly less than 40%, with a doubtful advantage over no additional treatment with the drug. Doxorubicin maintenance is clearly of no additional value.

2.1.3 Mitomycin

Mitomycin has a molecular weight of 329 and thus is absorbed only to a small extent. The dose varies between 20 and 60mg per instillation. In a recent review, the adverse-effects of leucopenia and thrombocytopenia were both found in only 4 of 613 (0.7%) patients.[10] A more frequent adverse effect is chemical cystitis, which is seen in approximately 15% of patients.[10] In our series, drug-induced cystitis and (culture proven) bacterial cystitis were seen in 20 to 25% of the patients.[22,23] Allergic reactions, mainly skin reactions such as palmar rash, are found in approximately 10%.[10,24] Most adverse effects disappear after cessation of therapy.

The overall success rates for definitive mitomycin therapy in papillary lesions is 43% (270 of 627) and for CIS 58% (51 of 88).[12] For prophylactic use, the advantage of mitomycin (15% higher success rate) over no treatment is not clear.[14] The advantage of mitomycin maintenance therapy is controversial.

In summary, systemic adverse effects for mitomycin are rare. The frequency of drug-induced cystitis is comparable to other chemotherapeutic drugs. In approximately 10% of the patients, (reversible) allergic reactions are seen. The response rates after mitomycin are around 50% and seem higher than of other chemotherapeutic agents. Our results with mitomycin have been better than the results in most other reports.

2.1.4 Etoglucid

Experience with etoglucid in superficial bladder cancer is limited. With a molecular weight of 262, it is poorly absorbed and systemic adverse effects are rare. The EORTC-GU group (study 30790) found exactly the same yearly recurrence rate (0.29) for intravesical therapy with doxorubicin (n = 165) and etoglucid (n = 156).[25] This was significantly better than the yearly recurrence rate of 0.65 in the control group (n = 70).

2.1.5 Epirubicin

Experience with epirubicin is increasing. To date, its reported adverse events seem mild. Mild chemical cystitis has been observed in approximately 15% of patients, while systemic toxicity appears to be absent.[26] In an EORTC study with a single immediate instillation of 80mg of epirubicin, chemical cystitis was only seen in 6.8% of patients.[27] The efficacy of epirubicin was significantly better than that of sterile water in patients with a single superficial tumour ($p < 0.0001$).

In summary, toxicity of epirubicin seems limited to drug-induced cystitis and seems less frequent than with other drugs (15% or less). Results about the efficacy of epirubicin are as yet too preliminary.

Similarly, experience is very limited with other intravesical chemotherapeutics, such as cisplatin and mitoxantrone.

Several additional drugs have been used to improve the efficacy of intravesical chemotherapy.

In a bladder cancer cell line, an effort was made to improve cell kill by adding dimethyl sulfoxide (DMSO).[28] However, the addition of 4% DMSO to 4 frequently used intravesical drugs failed to improve cytotoxicity. Recently, it was even suggested that intravesical DMSO might promote bladder carcinogenesis in mice.[29]

Verapamil is a calcium antagonist which can reverse multi-drug resistance (MDR). *In vitro* verapamil increased the cytotoxicity of doxorubicin by

a factor of 2.5.[30] Preliminary clinical data on the intravesical use of verapamil, however, have shown it to confer neither an additional advantage, nor to produce increased toxicity.[31]

2.2 Intravesical Immunotherapy

In 1976, the era of intravesical immunotherapy started with the introduction of intravesical bacillus Calmette-Guerin (BCG).[32] Since then, several other immunotherapeutic drugs have been used (interferon, interleukins, keyhole-limpet haemocyanin, bropirimine), although in limited (by the number of patients) clinical studies.

2.2.1 Interferon

Clinical experience to date with intravesical interferon in superficial bladder cancers is very limited. The optimal dose remains a question, and clinical results have been less than those observed with BCG.[33,34]

2.2.2 Bacillus Calmette-Guerin (BCG)

The mechanism of action of BCG remains unclear. There is a combination of a clear inflammatory effect (the nonimmunological response) and a nonspecific and specific immunological response (humoral and cellular).

The optimal dose seems to be 5×10^8 to 5×10^9 colony-forming units (CFU), although similar success rates, with less toxicity, have been reported with very low doses of BCG,[35-37] even in high-risk patients.[38] Intravesical instillation of BCG is accepted as the best route of administration. Combination with intradermal administration does not improve the results.[39] After a complete TUR of a superficial tumour, the initial schedule is a course of 6 weekly instillations. In high-risk patients (recurrences, CIS, etc.), a second course of 6 instillations or maintenance therapy (e.g. monthly instillations for 1 year) can be given. Both regimens will improve the success rates. A second course seems most useful in patients who respond well to the initial course of BCG and ultimately have recurrent disease. However, in patients failing both courses, a significantly higher risk for muscle invasion by the cancer is found, so more aggressive therapy should be considered. Maintenance therapy has more local and systemic toxicity.[40]

Local adverse effects (cystitis-like complaints) are found in over 90% of the patients and increase with the number of instillations.[41] They are easily treated with nonsteroidal anti-inflammatory drugs. Haematuria, although seldom severe, is seen in 43% of patients. Systemic adverse effects such as fever (28%), malaise (24%) and nausea (8%) generally subside spontaneously. Severe adverse effects (fever >39.5°C, genital infections, haematuria, BCG pneumonia/hepatitis/sepsis) are seen in about 5% of all patients.[42] In these patients therapy should be stopped, and eventually antituberculous therapy should be started. Only few fatal complications have been encountered, and traumatic catheterisation seems to play an important role in these cases. Therefore, treatment should be postponed for one week in case of a traumatic catheterisation.

The clinical results of BCG have been good. With BCG the recurrence rate of more than 60% without additional therapy decreases to 35% or less with a minimal follow up of 1 year.[40] BCG is superior to intravesical chemotherapy, but at the cost of inducing more adverse effects. A recent SWOG study, for example, showed a clear significant advantage of BCG over mitomycin.[43] In two of our own studies, however, this advantage of BCG could not be confirmed.[22,23] In fact, mitomycin toxicity was significantly less in our trials. Patient selection, prognostic profile and differences in treatment schedules and dose can partly explain these conflicting results.

After an incomplete endoscopic resection, BCG can be used as therapy, with success rates of 60 to 70%. In case of CIS, the success rates of BCG vary between 42 and 83% (patients at least 1 year free of recurrences as seen on cystoscopy and cytology).[40]

Although at this moment BCG seems to be the drug of choice for high risk superficial TCC, many questions remain unanswered, especially about the mechanisms of action, the optimal dose and clinical schedule.

2.2.3 Bropirimine

In high-risk patients failing intravesical BCG, more aggressive treatment such as cystectomy seems inevitable because of the high risk of tumour progression to muscle invasive disease. For such patients oral bropirimine might be an alternative.

Bropirimine is a biological response modifier which influences both humoral and cell-mediated immune responses. Its activity approached that of BCG in an animal model.[44]

Adverse effects are mainly mild to moderate 'flu-like symptoms (fever, nausea, fatigue and headache). Cardiac dysrhythmias have been reported in patients with coexisting cardiac disease.[45]

In superficial bladder cancer, a phase II study was performed with a dose of 3000 mg/day (amended from 4500 mg/day because of the cardiac dysrhythmias).[46] In 47 evaluable patients, 26 complete responses (negative cystoscopy, cytology and biopsy) were seen (55%), also in some of the patients who were BCG failures.

3. Long Term Efficacy Results In Superficial Bladder Cancer

In a review of long term results of intravesical chemotherapy, the short term cancer recurrence rate decreased from 58 to 41% in a group of 2,799 patients receiving cancer chemotherapy [thiotepa (n = 1009), mitomycin (n = 859), doxorubicin (n = 722) and etoglucid (n = 209)] versus those receiving no treatment,[14] with comparable results for different drugs. This reduction in recurrence rate, however, disappeared within a period of 5 years. A meta-analysis of 4 European Organisation for Research and Treatment of Cancer (EORTC) and 2 Medical Research Council (MRC) trials, however, showed a long-term (median follow up 7.7 years) reduction of the recurrence rate after intravesical chemotherapy.[47] An advantage of intravesical chemotherapy in reducing tumour progression, a more important goal, could not be confirmed,[14,47,48] although interpretation and comparison of many studies should be done with caution because of a number of variables in the studies. Comparing the long term follow-up of 1938 treated patients with a group of 2607 untreated controls, drug treatment caused no significant progression or survival advantage.[14]

A combination of controlled studies (1423 patients) also failed to demonstrate an advantage: the progression rate was 6.6% for treated patients and 7.2% for controls. Although it remains a question why obvious reduction of recurrence rates does not influence progression, an explanation might be that intravesical chemotherapy does not reach the deeper layers of the bladder, where the potentially invasive tumours might originate.

BCG, on the other hand, seems to be the only drug which also reduces tumour progression and even bladder cancer death.[14,49] Lamm, for example, observed an improved survival in patients treated with maintenance therapy in responders to an initial 6-week course.[14]

4. Invasive Bladder Cancer

An interesting approach is the use of primary (neoadjuvant) chemotherapy in patients with locally advanced (≥pT2) bladder cancer. In spite of negative screening, many of these patients will have recurrent disease after treatment with curative intent (radical surgery or radiotherapy) dependent on the initial stage of the tumour. It is also known that combinations of chemotherapeutic agents based on cisplatin (C) and methotrexate (M), with vinblastine (V) or with vinblastine and doxorubicin (A) can give response rates of 55 to 70%, with complete remissions of 25% or more for CM, CMV and MVAC.[50-52] Theoretically, therefore, neoadjuvant chemotherapy prior to local definitive therapy has potential advantages, as was shown in phase II studies.[53]

The first results of randomised studies indicated that there might be some advantage of neoadjuvant chemotherapy. A Nordic study, for example, indicated a 15% overall survival advantage after neoadjuvant chemotherapy and cystectomy with a 5-year follow-up.[54] In a combined MRC/EORTC study, 975 patients with locally advanced bladder cancer were randomised for no or 3 cycles of CMV

(cisplatin 100 mg/m^2, methotrexate 30 mg/m^2 and vinblastine 4 mg/m^2; CMV) prior to definite surgical or radiation therapy. Preliminary results after a median follow up of 22 months showed no difference in survival between neoadjuvant CMV or no CMV [Hazard ratio (HR) 0.95, p = 0.63].[55] Overall disease-free 2-year survival rates were 51 versus 45% (HR = 0.84, p = 0.06), but this might have been due to arm-dependent biases in the time to diagnosis of the progression. In patients treated with cystectomy, CMV appears to have clear activity on the primary tumour (33 versus 12% pathological complete responses). This was also found by Logothetis et al.[56] They compared 5 postcystectomy courses of MVAC to a combination of 2 pre- and 3 postoperative courses. The second interim analysis showed no survival difference, but in the 'neoadjuvant' group 28 versus 2% pathological complete responders were seen (p = 0.004), improving local resectability or offering the possibility of organ preservation. In general, low tumour stage (pT2) and downstaging to pT0 are important prognostic factors for neoadjuvant chemotherapy.

Compared with neoadjuvant treatment, immediate adjuvant chemotherapy for proven locally advanced disease has the advantage that the pathological stage is precisely known at the moment of the start of the chemotherapy. A disadvantage, however, is that there is no measurable disease. Moreover, bowel in the urinary tract can absorb chemotherapeutic agents if not drained. Skinner et al. reported a randomised trial comparing adjuvant CISCA (cisplatin, cyclophosphamide and doxorubicin) treatment versus observation after radical cystectomy and lymph node dissection.[57] In all, 91 patients with T3, T4 or N+M0 tumours were randomised. There was a significant advantage in the treated group for time to progression (p = 0.001) and survival (p = 0.006), but the group was small and not uniform. Freiha et al. also found a progression advantage (freedom of progression 37 versus 12 months, p = 0.01) using 4 additional cycles of CMV in 50 patients with a median follow up of 62 months.[58] However, they did not find a significant survival advantage (median survival 63 versus 36 months, p = 0.32), possibly because some relapsing patients could also be salvaged by CMV chemotherapy.

5. Treatment of Disseminated Bladder Cancer

We are regularly confronted with patients who already have metastasised bladder cancer or a relapse after intended curative treatment. In these patients chemotherapy should be considered.

Since the first report in 1985, the MVAC regimen is now widely used in urinary tract cancers.[59] The initial response rates were very promising [CR 50%, and partial response (PR) 21%]. In a follow-up study CR and PR rates were both 36%.[60] Moreover, there was a significant survival advantage in the CR group: median survival of more than 38 months compared to 11 months in the PR group, and 8 months for the non-responders. The most favourable sites of metastases were lungs, followed by retroperitoneal lymph nodes and bone. In a randomised trial, Logothetis et al. found somewhat lower response rates, but response rates ($p < 0.05$) and survival (p = 0.0003) were significantly better than with CISCA.[61] In another randomised trial MVAC was shown to be significantly superior to cisplatin monotherapy with regard to response rate and survival (p = 0.0002).[62] In spite of these promising initial CR rates, however, the majority of patients in these series relapsed.

Toxicity of MVAC remains a major limiting factor. Different grades of myelotoxicity are seen in almost all patients, and subsequent treatment-related deaths due to a nadir sepsis have been reported. Other adverse effects are mucositis, nausea, vomiting, alopecia and renal toxicity. MVAC is significantly more toxic than cisplatin monotherapy.[62] Toxicity data of some studies, including our own experience, are listed in table I. MCV is less toxic than MVAC, and is therefore also widely used. Efficacy of MVAC and MCV have, however, never been compared in a randomised study. Carboplatin is less toxic than cisplatin, but it also seems to be less effective.[63]

Myelotoxicity during MVAC therapy can be prevented or diminished with haematopoietic growth factors, such as granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF). Moore et al.[64] found approximately 40% ≥ grade 3 granulocytopenia when the first 2 cycles of MVAC were combined with GM-CSF compared with 80% in their earlier experience. In addition, nadir platelet and granulocyte counts were significantly higher. An ongoing EORTC trial will give more insight in to the value of this regimen.

In patients relapsing after MVAC chemotherapy the possibilities are very limited. Based on some promising results of Logothetis,[65] the EORTC has started a phase II trial to study the efficacy of a combination of fluorouracil, cisplatin and interferon-α as second-line therapy in patients with progressive metastatic transitional cell carcinoma of the urinary tract despite previous chemotherapy.

Testing of new drugs as a single agent (like gemcitabine) or in cisplatin-based combinations (like paclitaxel, vincristine, etoposide or ifosfamide) is ongoing. Results, however, are too preliminary to draw any conclusions about their efficacy or toxicity.

6. Conclusions and Recommendations

The question of drug therapy in superficial, invasive and metastasised bladder cancer remains difficult because results of clinical trials, to date, have not reached a consensus on all patients.

In patients with superficial bladder tumours at low risk for recurrence and progression, the initial transurethral resection should be followed by no or only one immediate intravesical instillation with a chemotherapeutic drug to prevent a recurrence due to tumour cell implantation during transurethral resection. Efficacy of this regimen has been clearly demonstrated and side effects have been very limited. Intermediate risk patients should receive a

Table I. Toxicity data of some MVAC studies

	Reference			
	Sternberg et al.[60]	Tannock et al.[66]	Loerher et al.[62]	Witjes et al.[67]
No. of patients	121	41	126	28
Leucopenia	GI: 7% GII: 27% GIII: 38% GIV: 20% Sepsis: 25%	<0.5: 90% Sepsis: 41%	GIII or IV: 24% Sepsis: 6%	GI: 20% GII: 40-50% GIII: 20-30%
Nausea, vomiting	GI: 45% GII: 21% GIII: 7%	6 (15%) Admission	GIII or IV: 12%	±100% usually mild
Nephrotoxicity	GI: 29% GII: 7% GIII: 2%	>1.5: 34% >2.0: 17%	GIII or IV: 7%	GI-II: 10-20% (2 patients stopped treatment[a])
Mucositis	GI: 19% GII: 17% GIII: 12% GIV: 1%	Mild: 17% Moderate to severe: 15%	GIII or IV: 17%	Mild in 23/28 (82%)
Neurotoxicity	GI: 2% GII: 1%		GIII or IV: 5%	1 (3.6%)
Toxic death	3 (4%)	1 (sepsis)	5 (4%) (4 due to sepsis)	1 (sepsis)[b]

a Kidney function at start already borderline.

b Second death during therapy from an intestinal bleeding with normal laboratory values and a complete response.

Abbreviations and symbols: MVAC = methotrexate, vinblastine, doxorubicin and cisplatin; GI = Grade I; GII = Grade II; GIII = Grade III; GIV = Grade IV.

course of additional intravesical instillations with mitomycin to lower the recurrence rate. We have found mitomycin to be effective with few and reversible adverse effects. However, although all chemotherpeutic drugs appear to be equally effective on a short term basis, their long term (5 years and more) effects with regard to recurrence and progression remains a question. In high risk patients intravesical immunotherapy with BCG is the standard preferred treatment. Although toxicity with BCG is more pronounced, it is usually mild and reversible with cessation of drug therapy. Maintenance BCG therapy seems to be able to decrease the tumour progression rate and therefore improve tumour-related survival.

The value of neoadjuvant systemic chemotherapy in patients with non-metastasised invasive bladder tumours has not been proven. Adjuvant chemotherapy immediately after surgery or radiotherapy remains in the experimental stage, and thus results of ongoing trials are needed. For metastasised or recurrent urothelial cell carcinoma, MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) remains the most effective treatment modality despite considerable and limiting systemic toxicity (predominantly leucopenia). Initial response rates between 40 and 70% can be achieved, although most patients will ultimately suffer a recurrence of their cancer.

References

1. Incidence of cancer in the Netherlands: 1992. Netherlands Cancer Registry, Utrecht, 1992
2. Kiemeney LALM, Straatman H, Witjes JA. Decreasing bladder cancer mortality in the Netherlands. Br J Urol 1996; 78: 686-90
3. Kiemeney LALM, Witjes JA, Verbeek ALM, et al. The clinical epidemiology of superficial bladder cancer. Observations among 1745 cases. Br J Cancer 1993; 67: 806-12
4. Lamm DL, Griffith JG. The place of intravesical chemotherapy as defined by results of prospective randomized studies (substances and treatment schemes). Prog Clin Biol Res 1992; 378: 43-53
5. Soloway MS. Selecting initial therapy for bladder cancer. Cancer 1987; 60 Suppl.: 502-13
6. American Cancer Society. Cancer facts and figures. Atlanta: American Cancer Society, 1991
7. Witjes JA, Kiemeney LALM, Oosterhof GON, et al. Prognostic factors in superficial bladder cancer. A review. Eur Urol 1992; 21: 89-97
8. Morrison DA, Murphy WM, Ford KS, et al. Surveillance of stage 0, grade I bladder cancer by cytology alone: is it acceptable? J Urol; 1984; 132: 672-4
9. Koontz Jr WW, Prout GR, Smith W, et al. The use of intravesical thiotepa in the management of non invasive carcinoma of the bladder. J Urol 1981; 125: 307-12
10. Thrasher JB, Crawford ED. Complications of intravesical chemotherapy. Urol Clin North Am 1992; 19: 529-39
11. Richie JP. Intravesical chemotherapy. Treatment selection, techniques, and results. Urol Clin North Am 1992; 19: 521-7
12. Bouffioux C, Meijden A vd, Kurth KH, et al. Objective response of superficial bladder tumors to intravesical treatment (including review of response of marker lesions). Prog Clin Biol Res 1992; 378: 29-42
13. MRC. The effect of intravesical thiotepa on the recurrence rate of newly diagnosed superficial bladder cancer. An MRC study. Br J Urol 1985; 57: 680-5
14. Lamm DL. Long term results of intravesical therapy for superficial bladder cancer. Urol Clin North Am 1992; 19: 573-80
15. Schulman C, Robinson M, Denis L, et al. Prophylactic chemotherapy of superficial transitional cell bladder carcinoma: an EORTC randomized trial comparing thiotepa, an epipodophyllotoxin (VM 26) and TUR alone. Eur Urol 1982; 8: 207-12
16. Novak R, Kern J, Fister H, et al. Effects of local chemotherapy and immunotherapy on the recurrence and progression of superficial bladder cancer. Eur Urol 1988; 14: 367-70
17. Martinez-Pineiro JA, Jimenez León J, Martinez-Pineiro L Jr, et al. Bacillus Calmette-Guerin versus doxorubicin versus thiotepa: a randomized prospective study in 202 patients with superficial bladder cancer. J Urol 1990; 143: 502-6
18. Llopis B, Gallego J, Mompo JA, et al. Thiotepa versus adriamycin versus cis-platinum in the intravesical prophylaxis of superficial bladder tumors. Eur Urol 1985; 11: 73-8
19. Crawford ED, McKenzie D, Mansson W, et al. Adverse reactions to the intravesical administration of doxorubicin hydrochloride: a report of six cases. J Urol 1986; 136: 668-9
20. Akaza H, Isaka S, Koiso K, et al. Comparative analysis of short-term and long-term prophylactic intravesical chemotherapy of superficial bladder cancer. Cancer Chemother Pharmacol 1987; 20: S91-95
21. Matsumura Y, Akaze H, Isaka S, et al. The 4th study of prophylactic intravesical chemotherapy with adriamycin in the treatment of superficial bladder cancer: the experience of the Japanese urological cancer research group for adriamycin. Cancer Chemother Pharmacol 1992; 30: S10-14
22. Debruyne FMJ, vd Meijden APM, Witjes JA, et al. Bacillus Calmette-Guerin versus mitomycin-C intravesical therapy in superficial bladder cancer. Results of a randomized trial after 21 months of follow up. Urology 1992, 40 Suppl.: 11-5
23. Witjes JA, vd Meijden APM, Witjes WPJ, et al. A randomized prospective study comparing intravesical instillations of mitomycin-C, BCG-Tice, and BCG-RIVM in pTa-pT1 tumors and primary carcinoma in situ of the urinary bladder. Intravesical instillations in superficial bladder cancer. Eur J Cancer 1993; 29A: 1672-6
24. de Groot AC, Meijden APM vd, Conemans JMH et al. Frequency and nature of cutaneous reactions to intravesical instillation of mitomycin for superficial bladder cancer. Urology 1992; 40 Suppl.: 16-9
25. Meijden APM vd, Kurth KH, Oosterlink W, et al. Intravesical therapy with adriamycin and 4-epirubicin for superficial bladder cancer: the experience of the EORTC GU group. Cancer Chemother Pharmacol 1992; 30: S95-98

26. Burk K, Kurth KH, Newling D. Epirubicin in treatment and recurrence prophylaxis of patients with superficial bladder cancer. Prog Clin Biol Res 1989; 303: 423-34
27. Oosterlinck W, Kurth KH, Schroder F, et al. A prospective European Organisation for Research and Treatment of Cancer Genitourinary group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single Ta, T1 papillary carcinoma of the bladder. J Urol 1993; 149: 749-52
28. Walker L, Walker MC, Parris CN, et al. Intravesical chemotherapy: combination with dimethyl sulfoxide does not enhance cytotoxicity *in vitro*. Urol Res 1988; 16: 329-31
29. Ohtani M, Miyanage N, Imada S, et al. Promotive effect of intravesical instillation of dimethylsulfoxide on bladder carcinogenesis in mice. Abstract. J Urol 1994; 151: 391A
30. Long JP, Prout Jr GR, Yau Kai Wong, et al. The effect of verapamil on multi-drug resistant bladder carcinoma cell line and its potential as an intravesical chemotherapeutic agent. J Urol 1990; 143: 1053-6
31. Ohi Y, Ohmori H, Shirahama T, et al. Intravesical instillation of adriamycin an the presence or absence of verapamil for the treatment of superficial bladder cancer: preliminary report of a collaborative study. Cancer Chemother Pharmacol 1992; 30: S50-54
32. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 1976; 116: 180-3
33. Glashan RW. A randomized controlled study of intravesical a-2b-interferon in carcinoma in situ of the bladder. J Urol 1990; 144: 658-61
34. Chodak GW. Intravesical interferon treatment of superficial bladder cancer. Urology 1989; 34: 84-96
35. Corti Ortiz D, Rivera Garay P, Aviles Jasse J, et al. Profilaxis del cancer vesical superficial con 1 mg de BCG endovesical: comparacion con otras dosis. Actas Urol Esp 1993; 17: 239-42
36. Martinez-Pineiro JA, Solsona E, Flores N, et al: Improving the safety of BCG immunotherapy by dose reduction. Eur Urol 1995; 27 Suppl. 1: 13-8
37. Pagano F, Bassi P, Piazza N, et al. Improving the efficacy of BCG immunotherapy by dose reduction. Eur Urol 1995; 27 Suppl. 1: 19-22
38. Mack D, Frick J. Five year results of a phase II study with low-dose BCG therapy in high risk superficial bladder cancer. Urology 1995; 45: 958-61
39. Witjes JA, Fransen MPH, v d Meijden APM, et al. Use of maintenance intravesical bacillus Calmette-Guerin (BCG), with or without intradermal BCG, in patients with recurrent superficial bladder cancer. Long term follow up of a randomised phase 2 study. Urol Int 1993; 51: 67-72
40. Witjes JA, vd Meijden APM, Debruyne FMJ. Use of intravesical Bacillus Calmette-Guerin in the treatment of superficial transitional cell carcinoma of the bladder: an overview. Urol Int 1990; 45: 129-36
41. Lamm DL, Stogdill VD, Stogdill BJ, et al. Complications of bacillus Calmette-Guerin immunotherapy in 1278 patients with bladder cancer. J Urol 1986; 135: 272-4
42. Lamm DL, Crissman J, Blumenstein B, et al. Complications of bacillus Calmette-Guerin immunotherapy: review of 2602 patients and comparison of chemotherapy complications. In: Debruyne FMJ, Denis L, vd Meijden APM, editors. EORTC Genito-Urinary Group Monograph 6: BCG in Superficial bladder cancer. New York: Alan R. Liss Inc., 1989: 335-55
43. Lamm DL, Blumenstein BA, Crawford ED, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacillus Calmette-Guerin for transitional-cell carcinoma of the bladder. N Engl J Med 1991; 325: 1205-9
44. Simmons WB, Reichert DF, Lucio RM, et al. Pyrimidinone Interferon Inducers in the Treatment of Murine Transitional Cell Carcinoma. J Urol 1983; 129: 169
45. Sarosdy MF, Lamm DL, Williams RD, et al. Phase I trial of oral bropirimine in superficial bladder cancer. J Urol 1992; 147: 31-3
46. Sarosdy MF, Lowe BA, Schellhammer PF, et al. Bropirimine immunotherapy of bladder CIS: positive phase II results of an oral interferon. Abstract. J Urol 1994; 151: 304A
47. Pawinski A, Bouffioux C, Sylvester R, et al. Meta-analysis of EORTC/MRC randomised clinical trials for the prophylactic treatment of Ta,T1 bladder cancer. J Urol 1996; 155: 492A
48. Akaza H, Kioso K, Kotake T, et al. Long-term results of intravesical chemoprophylaxis of superficial bladder cancer: experience of the Japanese Urological Cancer Research Group for Adriamycin. Cancer Chemother Pharmacol 1992; 30: S15-20
49. Herr HW, Wartinger DD, Fair WR, et al. Bacillus Calmette-Guerin therapy for superficial bladder cancer: a 10-year follow up. J Urol 1992; 147: 1020-3
50. Harker WG, Meyers FJ, Frieha FS, et al. Cisplatin, metotrexate and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. J Clin Oncol 1985; 3: 1463-70
51. Sternberg CN, Yagoda A, Scher HI, et al. M-VAC (metotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 1988; 139: 461-9
52. Stoter G, Splinter TAW, Child JA, et al. Combination chemotherapy with cisplatin and metotrexate in advanced transitional cell cancer of the bladder. J Urol 1987; 137: 663-7
53. Scher HI, Yagoda A, Herr HW, et al. Neoadjuvant M-VAC (metotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. J Urol 1988; 139: 470-4
54. Malmstrom PU, Rintala E, Wahlqvist R, et al. Five year follow up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic cystectomy trial I. J Urol 1996; 155: 1903-6
55. Hall RR. Neo-adjuvant CMV chemotherapy and cystectomy or radiotherapy in muscle invasive bladder cancer. First analysis of MRC/EORTC intercontinental trial. Abstract. Proceedings ASCO 1996. J Clin Oncol 1996; 15: 244
56. Logothetis C, Swanson D, Amato R, et al. Optimal delivery of perioperative chemotherapy: preliminary results of a randomized, prospective, comparative trial of preoperative and postoperative chemotherapy for invasive bladder carcinoma. J Urol 1996; 155: 1241-5
57. Skinner DG, Daniels JR, Russel CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991; 145: 459-67
58. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996; 155: 504-5
59. Sternberg CN, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 1985; 133: 403-7
60. Sternberg CN, Yagoda A, Scher HI, et al. M-VAC for advanced transitional cell carcinoma of the urothelium: efficacy and patterns of response. Cancer 1989; 64: 2448-58

61. Logothetis CJ, Dexeus FH, Finn FH, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990; 8: 1050-5
62. Loerher PJ, Einhorn LH, Elson PH, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine and doxorubicin in patients with metastatic urothelial carcinoma. A Cooperative group study. J Clin Oncol 1992; 10: 1066-73
63. Petrioli R, Frediani B, Manganelli A, et al. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent of metastatic bladder cancer patients. A randomized phase II study. Cancer 1996; 77: 244-51
64. Moore MJ, Iscoe N, Tannock IF. A phase II study of methotrexate, vinblastine, doxorubicin and cisplatin plus recombinant human granulocyte-macrophage colony stimulating factors in patients with advanced transitional cell carcinoma. J Urol 1993; 150: 1131-4
65. Logothetis C, Dieringer P, Ellerehorst J, et al. A 61% response rate with 5-fluorouracil, interferon-alpha2b and cisplatin in metastatic chemotherapy refractory transitional cell carcinoma. Proc AACR 1992; 33: 221
66. Tannock I, Gospodarowicz M, Connolly J, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy for transitional cell carcinoma: the princess Margaret hospital experience. J Urol 1989; 142: 289-92
67. Witjes JA, Wullink M, Oosterhof GON, et al. Toxicity and results of MVAC chemotherapy in advanced transitional cell carcinoma. Eur Urol. In press

Correspondence and reprints: Dr *J.A. Witjes*, Department of Urology, University Hospital, Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.