The Treatment of Non–Muscle-Invasive Bladder Cancer with Intravesical Chemotherapy and Immunotherapy

Peter Whelan
Department of Urology, St James’s University Hospital, Leeds, United Kingdom

1. Introduction

Seventy percent of patients with a diagnosis of bladder cancer present with non–muscle-invasive lesions that are now categorised as either of low or high malignant potential, though previously all were treated as superficial bladder cancer from TA to T1 and had frequently included carcinoma in situ (CIS). The new definition may make it easier to define those patients with lesions of high malignant potential, but much of the work on which we will base treatment that we offer to patients has the old pathologic categories and generically is grouped together as superficial bladder cancer. The important thing about these lesions, whether of high or low malignant potential, is that between 50% and 70% of them will recur within 5 yr after the initial transurethral resection (TUR) and that a number will inevitably progress to muscle-invasive disease [1]
2. Principles of intravesical therapy

The principles of intravesical therapy include:

- Prophylaxis, which is the prevention of new recurrences after complete resection of all visible tumours
- Therapeutic, which treats residual and resected or unresectable lesions

The goals in intravesical chemotherapy and immunotherapy are:

- To eradicate existing disease
- To inhibit tumour recurrence
- To prevent tumour progression
- To prolong survival

Risk factors that are being identified as tending towards possible muscle-invasive disease are:

- Multiple recurrences or multiple tumours at presentation
- A high recurrence rate
- Stage T1 or the presence of concomitant CIS
- A high grade
- Adjacent dysplasia not amounting to CIS
- Positive cytology in the absence of visible tumour
- Positive prostatic urethral biopsies
- A large size at initial presentation, that is, >5 cm.

Numerous problems and questions remain related to the optimal treatment and indeed the optimal regimen for any intravesical therapy. We do not know when instillation should start although most chemotherapy regimens recommend starting within the first few hours following resection; we do not know the optimal number of installations and most regimens have been determined on an empirical basis. The most important objective in treating superficial bladder cancer is to prevent progression to muscle-invasive disease. This, however, has proved tantalisingly difficult when we are often largely ignorant of what the optimal conditions are in the bladder for the best activity from an intravesical agent.

We know that all drugs are dependent on their lipotoxicity, their pH, the osmolality, the drug concentration, and the dosing volume and time relationships to that concentration passing over the affected area. Most treatment schedules have tended to be convenient for the patient and to follow an outpatient regime. They are, therefore, frequently, weekly × 4, monthly × 6 or 11, or a course of 6 weekly installations. With immunotherapy following the original report by Morales et al [2] in which 6 weekly installations were used, this has now become the standard.

In 1996, Pawinski et al [3] carried out meta-analysis of four trials by the European Organization for Research and Treatment of Cancer (EORTC) and two by the Medical Research Council (MRC) with a combined total of 2535 patients who were treated with either TUR alone or a TUR plus intravesical chemotherapy. The results of the meta-analysis showed a reduction in recurrence rates with therapy and that this was sustained to a median follow-up period of 7.7 yr, but there was no benefit in preventing progression. The intravesical agents used in these studies were either adriamycin, epirubicin, or mitomycin C and there appear to be no specific differences in these agents. Of equal importance was the study by Oosterlinck et al [4], which showed that a single instillation of the chemotherapeutic agent, in this case epirubicin, led to a 50% reduction in the recurrence rate but did not affect progression rates. Mitomycin C has been shown to be similar.

The three main factors that appear to determine a patient's ultimate prognosis remain tumour size at presentation, the grade, and the prior recurrence rate per year. Using these risk factors Kurth et al [5] constructed three groups of high-, intermediate- and low-risk patients in an analysis of 576 cases. In the high-risk group, which represented 38 of the 576 patients, there was a 41% progression rate and a 36% cancer death rate. In the intermediate group with 259 of the 576 patients, 17.4% progressed and there was a 12% cancer death rate, whereas in the low-risk category in which only one of the risk factors was present, there was a 7.1% progression rate and a 4.3% cancer death rate. This paper, together with a subsequent meta-analysis by Pawinski et al [3], demonstrated it was possible to define high-, intermediate-, and low-risk patients and that high-risk patients with a significant chance of both progression and death needed aggressive treatment and, therefore, the search for whether or not intravesical therapy would prevent progression was continued.

It is important to realise, before we assume that tumours of low malignant potential in the new scheme are not of significant risk, to review the low-risk group of Pawinski et al [3], which still had a 4% cancer death rate and a 7% progression rate, emphasising that these cannot be dismissed as benign papillomas.

patients who had pT1 G3 tumours treated by BCG and indicated that at 10 yr one third of these patients had died of bladder cancer, one third had died of other disease, but one third were alive and well with prevention of further progression and these patients had an intact bladder with no evidence of disease. There were sufficient suggestions that BCG may be superior to intravesical chemotherapy, with the crucial effect of preventing progression disease and, therefore, ultimately death.

In November 2002, Sylvester et al [8] carried out a meta-analysis of the published results of randomised clinical trials involving BCG to assess whether or not BCG had an effect on disease progression and ultimately death from bladder cancer. The meta-analysis initially started out with a total of 76 publications or abstracts but 52 of these were discarded and eventually 24 trials were evaluated as an additional trial. Meta-analysis showed that intravesical BCG treatment following TUR reduced the risk of progression in papillary tumours and CIS when maintenance BCG was used. The percentage of patients with progression was low, 6.4% in patients with papillary tumours and 13.9% with CIS. Only correspondingly small reductions in absolute percentage of patients with progression on BCG was observed, a reduction of 3% in patients with papillary tumours and 4.4% in CIS. However, it does appear that the effects of BCG in preventing progression in this meta-analysis are the same as its effectiveness in CIS. The one problem with this meta-analysis is that many of the papers included in the analysis had a very short follow-up of only 2.5 yr and, as we know from the longitudinal study of Herr et al [7], progression can occur some years later. It did not seem to make any difference what the schedule of the maintenance was, it just seems to be important from the meta-analysis perspective that at least maintenance was occurring.

However, in 2005 a review from the Cochrane Collaboration compared BCG with mitomycin C and concluded that BCG only reduced recurrence in high-risk cancers and had no effect on progression or survival when compared with mitomycin C. This shows that even the tool of meta-analysis has to be critically examined because these analysed studies were performed in the 1980s and 1990s and different BCG strains were compared with mitomycin C and in several published series, no difference between BCG and mitomycin C was demonstrated.

The effectiveness of mitomycin C in relation to progression may, in fact, have been diluted because of its lack of effective usage. In 1975, the original Moshina regimen [9] scheduled a total of 21 instillations over 7 wk for mitomycin and showed a complete response rate of 96%. The intensity of this regimen is rarely, if ever, used now, and it is quite possible that an effective drug has not been used optimally.

3. Conclusions

Mitomycin C and BCG are effective agents in both preventing recurrence and progression. It is customary to use mitomycin C in the perceived less aggressive lesions and BCG for higher risk patients, especially those with CIS. Additional benefit may be obtained from BCG by the addition of interferon-α but if bladder preservation strategies are to be used then a review of previous more aggressive regimens needs to be conducted and consideration given to the concentration, length of lesion exposure, the pH, and the temperature at which the chemicals are infused into the bladder. It remains possible that mechanical devices that enable a higher concentration of mitomycin C to be located within the superficial cells of the bladder mucosa may well be a further method of optimising the benefits this drug may give. Further research on all aspects of these possibilities is urgently needed.

References

