**Intravesical therapy of bladder cancer: An immunotherapy success story**

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Newly found superficial papillary transitional cell carcinoma (TCC) of the bladder is treated successfully with endoscopic surgery. However, these neoplasms are recognized for their tendency to recur in space and time (polychronotropism) and when they demonstrate a biological behavior with a propensity for recurrence, intravesical therapy has been advocated. A histologically different TCC, carcinoma-in-situ (CIS) of the bladder frequently carries a grave prognosis due to its tendency to metastasize early, and was most appropriately treated by radical cystectomy.

Initially a variety of cytotoxic chemotherapeutic agents were used with variable degrees of success and some of them are still widely used with satisfactory results. Most of these agents, however, exhibited little activity against CIS. The relatively small volume and ready accessibility of these neoplasms makes CIS, as well as the papillary lesions, ideal candidates for treatment with biological response modifiers (BRMs). The introduction, almost 20 years ago, of non-specific immunotherapy showing the effectiveness of bacillus Calmette-Guerin (BCG) not only resulted in a profound change in the management of bladder cancer, but in a renewed interest in the treatment of solid neoplasm.

**BCG AND BLADDER CANCER**

Superficial bladder cancer fulfills the criteria for successful immunotherapy:

- a. relatively small tumor burden
- b. direct contact between the agent and the neoplasm
- c. local administration of adequate doses
- d. good tolerance

Experience with the intravesical use of BCG for bladder malignancies now extends worldwide and the results universally demonstrate anti-neoplastic activity. Furthermore, the response rates, with a few exceptions have been comparable. Perhaps the most remarkable feature of the vaccine is that its effectiveness is so constant despite the variety of manufacturers in many countries and the variety of therapeutic regimens employed by different investigators.

**Prophylaxis of tumor recurrence.** The most encouraging results, reported using a BCG regimen involving an induction period of weekly administration followed by quarterly maintenance therapy demonstrated that BCG treatment is capable of preventing tumor recurrences in over 85% of patients with a history of papillary, non-invasive, bladder cancer.

**Carcinoma in Situ.** The most impressive results are those obtained in the therapy of CIS with intravesical administration of BCG. The initial report of complete responses in the vicinity of 70% have been a constant feature in the literature. However, these excellent results may be improved further by adding a maintenance regimen of administration.

There are differences of opinion among investigators regarding the effectiveness of BCG as compared to the mitomycin (MMC) cytotoxic chemotherapy. The current view is that there is little difference in effectiveness between the two agents in the treatment of small, well differentiated tumors. The superiority of BCG, however, is clear in the more anaplastic lesions and in CIS.

Despite the unsurpassed antineoplastic effect of BCG for bladder cancer, justified concerns exist over adverse side effects and potential complications. These concerns and measures...
to prevent occurrence of complications have been addressed. For instance, it is known that lower doses of BCG exhibit excellent anti-tumor activity but lower complication rate. It is evident that well trained personnel and thorough knowledge of the technique of administration makes these complications exceedingly rare. Treatment of the most serious problems is given in the table (Table).

INTERFERONS

For over a decade, intravesical interferons (IFN) have been used in small studies for the treatment of superficial bladder cancer but more recently they have gained increasing popularity. Early studies by the Northern California Oncology group, using recombinant interferon-alfa (IFN-α) in a small population, reported an overall response of 25% for papillary tumors, while the response in CIS was marginally better at 32%. More recently, Glassan et al. reported a dose-response study showing the effect of IFN-α in CIS. It appears, therefore that IFN-α despite exhibiting activity against TCC of the bladder does not reach the levels of activity observed with BCG. It has also been found that the activity of IFN-α is lower than the one observed for MMC. The main advantage of IFN-α is its excellent tolerance even at very high doses (>100 million units). Its cost, however, is high.

KEYHOLE-LYMPET HEMOCYANIN (KLH)

This compound has attracted intermittent interest as an effective immunotherapeutic agent for over two decades. It has been reported to be effective by intravesical administration. Its effectiveness has been under study for several years and, indeed, has been found to exhibit significant anti-neoplastic activity in superficial TCC. Results of a multicenter, North American study will be presented at the 1996 American Urological Association meeting.

MYCOBACTERIAL CELL WALLS (MCW)

Attempts to preserve the effectiveness of BCG with a non-living compound has directed attention to the use of mycobacterial walls. The concept is not new but until recently it met with little success. Studies continue on the use of such compounds as possible immunotherapeutic agents against cancer. We have explored the use of mycobacterial cell walls in experimental bladder and prostate tumors and are currently studying their effectiveness in the clinical setting.

BROPIRIMINE

This is an oral medication capable of interferon induction. Initial studies by Sarosdy et al. demonstrate significant anti-tumor activity in superficial bladder cancer. This drug is now the object of large multicenter, international trials.

CONCLUSION

Superficial bladder cancer is one of the few human solid tumors in which immunotherapy has proven to be effective. Newer regimens for BCG administration have decreased its toxicity and enhanced its effectiveness to astonishing levels. Newer and safer treatments are currently under investigation with promising results but their comparative value remains to be determined.

REFERENCES

2. Meng MV, Sanda MG. Comparison of intravesical BCG to radical cystectomy for high grade,


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<tr>
<td>TREATMENT RECOMMENDATION FOR BCG TOXICITY</td>
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<table>
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<tr>
<th>Condition</th>
<th>Treatment</th>
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<tr>
<td>Fever &gt; 38°C for &gt;48 hrs</td>
<td>INH 300mg x 3/12; Resume BCG when asymptomatic</td>
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<tr>
<td>Acute severe illness</td>
<td>INH 300mg; Rifampin 600mg; Ethambutol 1200mg; Daily x 6/12; No further BCG</td>
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<tr>
<td>Sepsis</td>
<td>As above; Cycloserine 500mg bid; Prednisolone 40mg IV acutely</td>
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