Preclinical Studies
of Monoclonal Antibodies
for Intravesical Radioimmunotherapy
of Human Bladder Cancer

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ABSTRACT

Eighty percent of bladder cancers present as superficial disease. Many are multifo
cal, and apparently successful treatment is frequently followed by recurrence. The use of monoclonal antibodies (MAbs) to
target radiotherapy to these tumors offers great potential, especially since they can be administered directly into the bladder (intravesically)
bypassing many of the side effects encountered to date with systemic MAAbased therapy. Implantation of human bladder cancer cell lines
in the bladder wall of nude rats results in tumor formation, providing an excellent model to test this. Tumor size can be monitored by X-ray
analysis after administration of urograffin. Comparative studies of two murine MAbs, BLCA-8, IgG3, and C1-137, IgG1, against malig
nant human bladder cancer cells have been performed. Radioimmunoconjugates produced with 125Iodine (125I) have been used for biodistribution studies following administration directly into rat

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bladder. Radioiodinated intact MAbs or Fabs administered intravesically into nontumor bearing rats did not leak into the systemic circulation and were stable in urine for up to 100 h. Biodistribution studies carried out following intravesical administration of radioimmunoconjugates to tumor-bearing nude rats indicate better tumor uptake of C1-137 than BLCA-8. Further studies to test two-step intravesical administration of biotinylated MAb followed by radioiodinated streptavidin are in progress. Our studies indicate that the C1-137 MAb may have considerable potential for intravesical radioimmunotherapy of patients with superficial bladder tumors.

Index Entries: Bladder cancer; monoclonal antibodies; radioimmunotherapy; intravesical administration; xenografts.

INTRODUCTION

Bladder cancer has a high and rising incidence (1). It can present as superficial (80%) or invasive (20%) disease, these forms following different natural courses (reviewed in 2). The disease occurs multifocally and has a high recurrence rate after apparently successful treatment. Immunotherapy, the local inoculation of Bacille Calmette Guerin (BCG) (3), either alone or with cytokines such as IL-2 (4), currently provides the best option for patients with superficial bladder cancer, but may be associated with some morbidity. Tumors may recur and progress, eventually resulting in death (2). An alternative treatment is the direct (intravesical) administration via a catheter of immunoconjugates, monoclonal antibodies (MAbs) linked to a therapeutic agent. Such treatment should bypass many problems associated with systemic therapy, such as localization of antibodies in normal tissues (5), failure to penetrate necrotic tumor tissue, and the stimulation of human antimouse antibody (HAMA) formation (6). Indeed, direct intravesical treatment of patients with superficial bladder cancer must represent the acid test for MAb-targeted therapy. Of several options for intravesical MAb-based therapy, we have selected radioimmunotherapy. Bladder cancer cells exhibit heterogeneity in their antigen expression (7). Radioimmunoconjugates do not need to be internalized (8) and their radioactivity can affect both targeted antigen-positive cells and adjacent antigen-negative cells. To be effective, radioimmunoconjugates must fulfill certain criteria. The antibody must be specific and of high affinity and its antigen must be expressed in a high proportion of tumors. For intravesical treatment, both the immunoconjugates and their target antigens must be stable in the urinary environment, and they must not leak from the bladder into the systemic circulation. This paper describes preclinical studies using two antihuman bladder cancer MAbs, C1-137 (IgG1), and BLCA-8 (IgG3) (9) in an animal model developed to evaluate intravesical radioimmunotherapy (10).