

RADIOMMUNOTHERAPY AND PROSTATE CANCER: A PROMISING NEW THERAPY IN THE MANAGEMENT OF METASTATIC DISEASE

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INTRODUCTION

The mainstay of treatment for metastatic prostate cancer is androgen deprivation, but unfortunately all patients eventually become resistant to this treatment, developing androgen-independent cancer, with a median time to death of ≈ 1 year. In addition, taxane-based chemotherapy has met with limited success and is usually associated with significant toxicity. Recent research has suggested that radioimmunotherapy (RIT) using radiolabelled monoclonal antibodies (mAbs) could emerge as a novel and potentially successful treatment for metastatic prostate cancer.

PRINCIPLES OF RIT

RIT is a systemic treatment which uses a mAb in addition to a radioisotope, which emits α or β particles, thus delivering radiation to tumour cells. Metastatic prostate cancer may be a suitable target for effective treatment using RIT for several reasons. First, metastases are found almost exclusively in bone marrow and lymph nodes, both of which have an abundant blood supply, thus allowing good access to mAbs. Second, metastases are usually small enough to allow good penetration of mAbs. In addition, many prostate tissue-specific antigens can be targeted, and the response to treatment can be rapidly measured using serum PSA levels.

IMPORTANT PROPERTIES OF RADIOISOTOPES

In RIT, the physical properties of radioisotopes need to be selected to take into account

the size of the target lesion, and the mAb targeting and internalization properties. These properties include the path length, energy emission and the physical half-life. For prostate cancer, the commonest isotopes in use are ^{90}Y and more recently, the lanthanide ^{177}Lu (^{177}Lu). ^{90}Y is a high-energy β -emitting radionuclide with a half-life of 64 h and can be produced in large amounts from a generator [1]. However, its wider range of action can result in normal tissue toxicity, and as it does not emit γ particles it is difficult to monitor its biodistribution. ^{177}Lu has high-energy β emission, a half-life of 6.65 days, a relatively small range (ideal for treating low-volume disease) and has γ emission, making it more suitable for imaging by γ -cameras. In addition, it can be cheaply produced in a reactor in very large amounts. There are ≈ 100 radioisotopes that decay with α -particle emission [2]. Isotopes emitting β particles are cytotoxic over a spherical volume with a radius that extends a few millimetres (maximum 11.0 mm for ^{90}Y). Thus by targeting several tumour cells, large lesions (2–3 cm) can be efficiently treated by means of the 'crossfire' effect [3]. By contrast, α -emissions occur over a short range, of 60–100 μm , and are more useful in the treatment of micrometastatic disease.

TARGET ANTIGENS IN PROSTATE CANCER

The selection of a suitable antigen on the surface of prostate cancer cells is one of the most critical factors in determining the success of RIT. Ideally, the target should be a cell-surface antigen, which is minimally shed or secreted, abundantly expressed by prostate cancer cells, with expression increased in high-grade and hormone-refractory tumours, and expression should be low in normal tissue. Using these criteria several potential antigens have been discovered [1,4]. Of these, prostate specific membrane antigen, now termed folate hydrolase (FOLH-1), a 750-amino acid stable glycoprotein, appears to be the most promising. It is highly expressed in

prostate cancer cells, and expression levels increase with more poorly differentiated bone and lymph node metastasis, as well as in hormone-refractory prostate cancer. Interestingly, FOLH-1 is also expressed in endothelial cells of tumour-associated neovasculature, including colon, breast, melanoma, lung, but not in normal vascular endothelium. The humanised mAb J591 binds to the extracellular domain of FOLH-1, and has the advantage of targeting both soft tissue and bone metastases, and importantly is not immunogenic; previous antibodies to FOLH-1 were associated with severe myelotoxicity.

STUDIES OF RIT IN PROSTATE CANCER

Several preclinical studies showed the effectiveness of radioisotopes emitting β -radiation [1]. Recently, Bander *et al.* [5] showed in a phase I trial, using ^{177}Lu -J591 in androgen-independent prostate cancer, that four of 35 patients (11%) had a decrease in PSA level lasting 3–8 months, and 16 (46%) had PSA stabilization for a median of 60 days. There was targeting of all known sites of bone and soft-tissue metastases in all 30 patients. In a further phase I trial, in which ^{90}Y -J591 was investigated, two of 29 patients (7%) had a decline in PSA level lasting 8 and 8.5 months, and six (21%) had stabilization of their PSA level [6]. There was targeting of known sites of bone and soft-tissue metastases in most patients. These trials suggest that ^{177}Lu -J591 might be better suited to treating small-volume lesions (<5 mm) whereas ^{90}Y was better for larger volume disease (>1 cm). Although encouraging, the results clearly need to be confirmed in larger phase II trials, which are imminent. Progress with radioisotopes emitting α -radiation are less advanced, although significant work showed extensive inhibition of prostate cancer cell lines *in vitro* in a concentration-dependent fashion, and *in vivo* studies confirmed complete inhibition of tumour growth in animal models [2]. It is expected that clinical studies will be published shortly.

Improvements in increasing the targeted radiation delivery to tumour sites are fundamental to the future success of RIT in prostate cancer. Attempts are being made to try multiple treatments, with dose and scheduling predicated on red marrow toxicity and recovery [7], or

to pre-target antibodies, whereby the tumour is pre-targeted with an antibody construct that has affinity for the tumour-associated antigen and for a radiolabelled hapten [8,9].

CONCLUSIONS

RIT for prostate cancer appears to be an exciting new treatment option for metastatic and hormone-refractory disease. Several tumour antigens are being used as targets, and preclinical and early phase I trials are showing some promising results. This treatment alone, or combined with chemotherapy [10], might provide the basis for a promising new therapy for treating metastatic prostate cancer.

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Abbreviations: RIT, radioimmunotherapy; mAb, radiolabelled monoclonal antibody; FOLH-1, folate hydrolase.