Monoclonal Antibodies in Cancer Treatment
A Review of Recent Progress

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Abstract
Research advances and promising clinical outcomes with immunotherapeutics has led to a resurgence of incorporating monoclonal antibodies in cancer treatment. Unconjugated, conjugated and multi-target constructs are emerging as a conventional form of therapy along with the classical trio of surgery, radiation and chemotherapy. The recent major accomplishments in monoclonals include: first, the development of human and chimeric structures negating the induction of humoral responses to murine counterparts which limited use; second, protein
The primary impetus behind the development of therapeutic and diagnostic strategies for cancer using monoclonal antibodies (mAbs) has been the specific targeting properties of these molecules, which can greatly reduce or limit unwanted toxicities to normal tissues. Initial clinical trials with mAbs had some impressive antitumour effects. The numerous trials which have followed have not as yet fulfilled the ‘magic bullet’ dream.

Antibodies may promote anti-tumour effects directly by inducing apoptosis, complement-mediated cytotoxicity, or antibody-directed cellular cytotoxicity, and indirectly by interfering with ligand-receptor interactions or through the induction of an anti-idiotype network. However, the potential housed in the unique specificity of a mAb for its tumour antigen epitope alone is not sufficient to guarantee a cytotoxic outcome. The obstacles encountered with using mAbs are now being realised and addressed. Factors that may impede the delivery of mAbs, their retention in the tumour and the antitumour events that occur after their binding to antigen include: tumour tissue architecture with its disordered vasculature and increased intratumoral hydrostatic pressure; tumour antigen distribution and epitope location; tumour microenvironment; and the host immune response. These factors have been reviewed.

Preclinical and clinical data with improved agents that address these impediments continue to demonstrate an emerging role for antibody-based therapy as a component of the oncological armamentarium. This article reviews the past 5 years of mAb clinical trials. Toxicities, responses, agent modifications and limitations encountered are addressed.

Significant responses have been observed in selected phase I trials – an arena where multiple pretreatment regimens and heavy tumour burden are the norm. The information accumulated from these studies suggests that the greatest benefit for many mAb-based therapies would be in a setting of minimal residual disease and in combination with other maintenance therapies. Future mAb-based therapies must consider the physical limitations for effective targeting and design trials that will optimise the parameters where efficacy has been shown.

1. Monoclonal Antibody Therapy as Single Agents

A variety of antibodies with different targets have been developed and tested (table I). Historically, therapies with mAbs as single agents have been well-tolerated. Commonly described adverse effects are transient fevers, rigors, pruritic rash and hypotension. In the past, therapy with mAbs has been hampered by the development of antibody species-specific immune responses. The development of technologies which can create chimaeric proteins, grafting the constant domains of human antibodies onto xenogeneic variable domains, will remove a major limitation to immunotherapies. Protocols with agents that can be admin-