Monoclonal Antibodies as Tumour Therapy
Clinical Evidence in Favour of Their Potential Usefulness

Robert O. Dillman
Hoag Cancer Center, Newport Beach, California, USA

Contents

Summary ................................................................. 206
1. Unmodified Monoclonal Antibodies .................................. 207
   1.1 Indirect Cytotoxicity ........................................ 207
   1.2 Direct Effects ................................................ 208
   1.3 Results of Clinical Trials .................................... 209
2. Immunoconjugates .................................................. 211
   2.1 Radiolabelled Monoclonal Antibodies ....................... 211
   2.2 Immunotoxins ................................................. 213
   2.3 Chemoimmunoconjugates ..................................... 214
   2.4 Cellular Conjugates ......................................... 214
3. Monoclonal Antibodies with Other Biological Response Modifiers .. 215
4. Issues and Future Directions ....................................... 215

Summary

Monoclonal antibodies (mAbs) may be useful as tumour therapy when used as homogeneous immunoglobulin, or as carriers of specific cytotoxic agents. mAbs directed against tumour may be indirectly cytotoxic by interactions with components of the immune system in antibody-dependent cell-mediated cytotoxicity or complement-mediated cytotoxicity. mAbs that bind to receptors on the membranes of tumour cells may alter the biological behaviour of tumours by blocking or downregulating growth factor systems essential to tumour cell proliferation.

The conjugation of radioisotopes to mAbs has already led to the approval of reagents for the radioimmunodetection of cancer. Therapeutic mAb radiopharmaceuticals have already shown great promise in radiosensitive lymphomas. Cytotoxic chemotherapeutic agents conjugated to antitumour mAbs may be processed intracellularly in such a way that they bypass some mechanisms of drug resistance. Immunotoxins, conjugates of natural toxins and mAbs, make possible site-specific delivery of highly toxic agents that cannot be used clinically in their natural state.

mAbs may stimulate receptors on host immune cells, such as the CD3 receptor on T lymphocytes, thereby activating those cells and increasing their cytotoxicity. mAbs can serve as targeting carriers of lymphokines and cytokines to selectively modulate the cytotoxic potential of immune cells in the microenvironment of a tumour.

If a sufficient large library of mAbs can be made available, physicians of the
future may combine various mAbs and immunoconjugates for highly selective combination therapy based on known antigenic tumour cell determinants and a knowledge of the host’s immune system.

The control of cancer is an ever-increasing challenge to healthcare providers throughout the world. In the US there are over 1 million new cancer cases diagnosed each year, and over 0.5 million deaths from cancer each year. In other words, more Americans die each year of cancer than American deaths in all of the wars of the twentieth century. The major cause of cancer death is metastatic disease, typically resulting from micrometastases that cannot be treated by the local modalities of surgery and radiation therapy. Thus, once cancer is diagnosed, the major challenge is how to treat metastatic cancer systemically. Two major limitations to existing systemic cancer therapies are their lack of specificity, especially for chemotherapy, and the intra- and inter-patient heterogeneity of cancer cells which results in varying degrees of susceptibility to systemic therapy. Because of their natural specificity, antibodies that react with tumour-specific or tumour-associated antigens could be useful in improving the therapeutic index of systemic cancer therapy.

In 1975 Kohler and Milstein described the secretion of monoclonal antibody (mAb) by a B cell hybridoma, and in 1984 they were awarded the Nobel Prize in Medicine for their pioneering work. Subsequently, biotechnology companies have produced sufficient quantities of mAbs for clinical investigation. During the past 10 to 15 years, numerous clinical trials have been conducted with mAbs in patients with cancer. The strategies for in vivo therapy that have been used are summarised in Table I. Most trials have been conducted utilising murine mAbs, but an increasing number of trials have been carried out using human, mouse/human (chimaeric) or humanised mAbs in which genetic engineering has been used to retain the murine determinants of antibody specificity while humanising the rest of the antibody molecule. The rationale for these approaches and the results of clinical trials with mAbs are summarised in this paper.

1. Unmodified Monoclonal Antibodies

1.1 Indirect Cytotoxicity

Some mAbs are able to fix complement or interact with cytolytic and/or phagocytic cells. They therefore cause lysis of cells that express distinct antigenic surface determinants.

Complement-dependent cytotoxicity involves fixation of complement to the Fc portion of the immunoglobulin molecule followed by activation of the complement cascade and the enzymatic destruction of the tumour cell membrane. Antibody-dependent cell-mediated cytotoxicity involves various effector cells. These include monocytes, macrophages, granulocytes, eosinophils, and certain lymphocytes which have Fc receptors that can adhere to the Fc portion of immunoglobulin molecules. Once such cells come in contact with tumour cells, they destroy tumour cell membranes enzymatically. Administered mAbs may bind to tumour cells, and subsequently circulating effector cells may attach to the exposed Fc portion of the immunoglobulin molecule. Alternatively, mAbs injected into the bloodstream may attach to circulating effector cells and subsequently bind to tumour cells.

Of the murine mAbs, the IgM class is most efficient in complement-dependent cytotoxicity, followed by the IgG3 subclass. Murine IgG2A, IgG1