EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Antineoplastic antibodies – clinical applications

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SYNOPSIS

Trastuzumab and rituximab are genetically engineered antibodies which are now available for the treatment of metastatic breast cancer and non-Hodgkin's lymphoma respectively. The adverse effects of these drugs are mild compared with conventional chemotherapy, but they require intravenous infusion in a supervised setting. Trastuzumab and rituximab are most effective when given with chemotherapy rather than as a substitute for standard therapies. Such combination therapy offers incremental but significant clinical improvements. The challenge remains to identify optimal antibody dosing schedules and the cancer subtypes which best respond to these treatments.

Key words: trastuzumab, rituximab, breast cancer, lymphoma.

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Introduction

The first monoclonal antibodies were generated, using hybridoma technology, almost three decades ago. The hope was that these 'magic bullets' would target cancer cells without damaging normal cells thus offering a clear advantage over conventional cancer treatments. Major trials using genetically engineered antibodies to treat non-Hodgkin's lymphoma and breast cancer have now been completed and it appears that the clinical utility of some antibodies has at last been realised. The results from these trials have changed old notions of the ideal therapeutic antibody. They show that monoclonal antibodies are most effective when used in combination with, rather than instead of, chemotherapy.

Mechanism of action of therapeutic anticancer antibodies

Antibodies are large molecules (150 KiloDaltons). They consist of a variable region, which binds specifically to a target antigen, and a constant region, which mediates a variety of effector functions such as cell-mediated killing and complement activation.

In their native form, unconjugated antibodies have a wide range of antitumour activities. Antibodies can directly influence tumour cell growth by blocking a growth factor receptor or they can cross link cell membrane antigens to deliver signals that control the cell cycle or even induce cell death. Alternatively, they can influence tumour growth indirectly by activating host immune effector functions such as antibody-dependent and complement-mediated cell cytotoxicity. Given the diversity of actions of unconjugated antibodies, it is often impossible to identify those specific actions which are operative in a given individual.

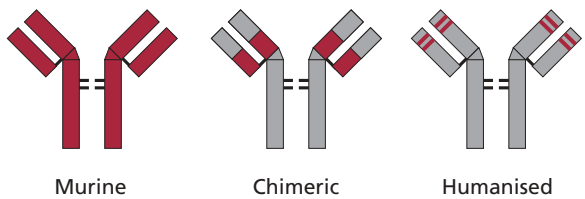
Antibodies raised in mice (murine) have significant disadvantages as therapeutic agents. They are immunogenic, a feature which limits their repeated administration, and they have poor cytotoxicity as their constant region does not interact with human effector cells.

Molecular techniques now make it possible to transform murine antibodies into human antibodies. A chimeric antibody is generated by substituting a human constant region (usually IgG1) for the murine constant region so that the new antibody is 60% human and 40% murine (Fig. 1). A further step on from a chimeric antibody is a humanised antibody (95% human and 5% murine). In this process the structural amino acids in the variable region as well as in the constant region are replaced by human sequences (Fig. 1). Only a small number of amino acids directly responsible for binding to the antigen are retained from the mouse antibody.

Coupling antibodies to cytotoxic agents such as drugs, toxins and radionuclides potentially links the unique specificity of antibodies with powerful tumouricidal activity. Despite the theoretical advantage of such an approach, there are as yet few practical examples of its implementation. One notable success is the use of a humanised anti-CD33 antibody (gemtuzumab) covalently linked to a derivative of a cytotoxic antibiotic, calicheamicin. This drug, called gemtuzumab ozogamicin, has shown activity in elderly patients with acute myeloid leukaemia who are unsuitable for conventional chemotherapy.

Fig. 1

The structure of a chimeric and humanised antibody compared with its mouse counterpart. The red indicates mouse, the grey represents human protein.



Trastuzumab – breast cancer

Trastuzumab is a humanised antibody which targets the HER2/*neu* receptor, a cell surface protein which is overexpressed in a proportion of breast cancers. Original reports suggested that HER2 was overexpressed in 20–30% of breast cancers and therefore a significant number of women would potentially benefit from trastuzumab. Unfortunately this figure was an overestimate; overexpression is probably closer to 10%.

Suitability for trastuzumab therapy is predicated on the accurate identification of HER2 overexpression. This presents a significant challenge as it requires specialised and expensive techniques such as immunostaining and fluorescent *in situ* hybridisation (FISH) analysis. Neither of these tests is perfect.

Trastuzumab is currently available in Australia for the treatment of HER2 positive tumours under two circumstances:

- monotherapy in women who have received one or more chemotherapeutic regimens for metastatic disease
- in combination with taxanes (such as paclitaxel) in women who have not previously received chemotherapy for metastatic disease.

Monotherapy

Approximately 15% of women with HER2 positive tumours have an objective response to weekly intravenous monotherapy.[1] This response rate is comparable to that seen with chemotherapy drugs such as paclitaxel (25%), docetaxel (35%), vinorelbine (22%), 5-fluorouracil (25%) and capecitabine (20%). While the incidence of serious toxicity is probably lower with trastuzumab, it is difficult to draw meaningful conclusions about the relative merits of each drug as they have not been directly compared in a single study. With regard to costs it is clear that drugs such as trastuzumab, paclitaxel and docetaxel are many times more expensive than capecitabine and 5-fluorouracil.

Combination therapy

As predicted by *in vitro* studies, there is considerable synergy between trastuzumab and chemotherapy. As first-line treatment for metastatic disease, the addition of trastuzumab to paclitaxel increases the response rate (complete and partial) from 17% to 41%, the median time to disease progression from 3.0 months to 6.9 months and the median survival from 20.3 to 25.1 months.[2] The precise impact of trastuzumab on overall survival may have been underestimated. A number of factors confound this analysis, for example, patients who were randomised to chemotherapy were permitted to receive trastuzumab subsequently once their cancer progressed.

Importantly, the clinical advantages of trastuzumab were obtained without additional negative effects on quality of life. Most treatment adverse effects were attributable to the chemotherapy. However, trastuzumab cannot be safely used with all chemotherapy. There was an unexpectedly high incidence of cardiac dysfunction (27% of patients) when the drug was combined with anthracyclines.

On balance, it is reasonable to conclude that the combination of trastuzumab and chemotherapy results in a modest improvement in response rates and probably overall survival in a very select group of women. As yet unresolved issues include the necessity for weekly antibody infusions, the best means of identifying women whose tumour growth is dependent upon HER2 overexpression, and the true value of trastuzumab in the adjuvant setting.

Rituximab – lymphoma

Rituximab was the first antibody to be approved by the US Food and Drug Administration for the treatment of malignancy. It is a chimeric antibody which binds strongly to the CD20 antigen found on normal mature B cells as well as on tumour cells in nearly all B cell non-Hodgkin's lymphomas.

Monotherapy

Low-grade lymphoma is a chronic illness usually requiring intermittent, but long-term, treatment to control disease symptoms. The listing of rituximab on the Pharmaceutical Benefits Scheme has expanded the range of therapeutic options for patients with low-grade lymphoma whose disease is not responsive to alkylating agents. The evidence supporting the use of rituximab was provided by an open label single arm phase III study. In the 151 evaluable patients who had previously received chemotherapy nine had complete responses and 67 had partial responses.[3]

Treatment with rituximab involves four infusions given at weekly intervals. A number of patients have received further courses of therapy with good effect.

Most patients experience fever, chills and rigors within two hours of commencing the first infusion. The incidence of infusion-related symptoms decreases to 40% with subsequent infusions. Approximately 10% of patients develop serious symptoms including immediate hypotension, bronchospasm and rarely a late onset cytokine release syndrome characterised by severe dyspnoea and hypoxia up to two days after the infusion. Rituximab binds to normal B cells which are the precursors of the immunoglobulin producing plasma cells. Serum immunoglobulin levels can fall after treatment, however this is not usually clinically significant.

In terms of relative therapeutic effect rituximab appears to offer comparable efficacy, but with less toxicity than intensive combination chemotherapy or drugs such as fludarabine. The optimal schedule of administration remains a key unresolved issue. Rituximab is detectable for three to six months following a single course of therapy so it is possible that infrequent single doses may provide maximum therapeutic effectiveness.

Combination therapy

About 30% of patients with non-Hodgkin's lymphoma have diffuse large B cell lymphoma, and more than half of these patients are over 60 years old. For about 25 years the standard treatment for this form of lymphoma has been a regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) given every three weeks for six months. Over the years more complicated combinations have been tried, but none have improved on the 30–40% cure rate observed with CHOP. The results of combination therapy with rituximab and CHOP have therefore sparked considerable interest.

The addition of rituximab to CHOP significantly improved the complete remission rate (75% versus 63%) and overall survival at two years (70.2% versus 57.3%) in patients aged between 60 and 80 years.[4] Importantly, these gains were made without apparent increase in overall toxicity.

The apparent success with combination therapy cannot yet be applied to all patients with lymphoma. Lymphoma is a heterogenous disease and the responses to treatment are clearly dependent upon a number of factors including the exact type of lymphoma and the age of the patient. For instance, there are currently no data supporting any role for the combination of rituximab and chemotherapy in people under 60 years old.

The cost of treatment needs consideration. One cycle of treatment with rituximab-CHOP costs approximately $4000 compared with $500 for CHOP alone. Another consideration is the new data which show that increasing the frequency of CHOP to fortnightly produces comparable improvements, in overall survival and complete remission rates, to those seen with rituximab-CHOP. Given these findings, and the cost of rituximab, it will be important to establish the optimal number of infusions, as well as the specific sub-group of patients for whom this drug is truly beneficial.

Conclusion

Therapeutic antibodies have not revolutionised the management of patients with cancer. However, the incremental gains associated with the use of these drugs have cemented their place in the clinical management of a select group of individuals. Over the next few years the precise role of these and other antibodies as adjuvant or first-line treatment for specific diseases will become apparent.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 151)

9. Trastuzumab is only indicated for women with breast cancers which overexpress the receptor HER2.
10. A serious adverse reaction to rituximab may not develop until two days after the infusion.

Book review

Australian Medicines Handbook Drug Choice Companion: Aged Care.

Adelaide: Australian Medicines Handbook; 2003.

218 pages. Price $50, students $45, plus postage.

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The Companion is intended for use in conjunction with the Australian Medicines Handbook (AMH), the well-known and highly valuable drug formulary. It aims to assist those working in aged care, especially in residential facilities. The nearly pocket sized volume with a ring binding is easy to handle and the cover is probably resistant to contamination by bodily fluids.

The text itself is organised into common clinical problems in the aged care setting, with dementia and other neurological conditions heading the list. Following the instructions inside the front cover, I used the index to trace my way through typical clinical questions. Each topic is subdivided into consistent subheadings that include diagnostic issues and non-drug issues. The subsections on 'evidence' are a neat way of giving credence to the book's assertions.

There are useful summaries on conditions that one meets much more often in nursing homes than in textbooks of medicine – restless legs syndrome, managing stroke risk in people with advanced morbidity, and (not) crushing or splitting tablets. Several practice points and warnings are highlighted as call-outs, an effective device to focus one's attention to key messages.

The brevity of the work does present difficulties, for example there is no evidence section under insomnia. In Parkinsonism the problem of a poor clinical response to dopaminergic therapy is clearly stated, but the difficulty of existing postural hypotension (such as in multisystem atrophy) being aggravated by the drugs, is only hinted at. I found the inclusion of the section on irritable bowel syndrome puzzling, given that it may be 'less common in older than in younger people' and 'convincing evidence for the efficacy of drug treatments… is lacking'. Disabling stroke is a difficult management problem in nursing homes and hostels and a section on the therapeutics of spasticity would have been useful.

The Companion reasonably succeeds in its aim of assisting the busy aged care worker at the bedside. Doctors, nurses and pharmacists, particularly those doing medication reviews, should find this extremely useful. It is a 'first of its kind' in Australia.