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Review

Monoclonal antibodies in the treatment of lung cancer

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Abstract

Background: Lung cancer is an aggressive disease and its conventional therapy is far from success. There is a strong need for new, better approaches to improve survival, symptom control and quality of life.
Methods: The authors searched the literature for indexed articles published over the past 30 years from Pubmed concentrating on all possibilities of monoclonal antibodies in the therapy of tumours and especially of lung cancer.
Results: The search resulted in more then 200 published articles. Important major reports of the pre-clinical/clinical investigations of monoclonal antibodies in the therapy of tumours, with an emphasis on lung cancer were reviewed, screened and tracked for other relevant publications and the yielded data were summarized and systematized.
Conclusion: It is concluded, that immunotherapy and the reviewed use of monoclonal antibodies in the therapy of tumours (including lung cancer) certainly carries a hope. However, studies of this topic are in a wide range of phases, from experiments to clinical trials, thereby their results are not comparable with each other. Based on the data available though the authors feel that active immunization with monoclonal antibodies as anti-idiotype vaccines, and antibody targeting with immunoconjugates (immunotoxins, radioimmunoconjugates and chemoimmunoconjugates) are the most promising methods. Radioimmunoguided surgery and immunoguided focal ablation are also valuable. Anti-growth factor monoclonal antibodies are the most evaluated agents so far. They certainly have an objective effect, though they are still not the 'magic bullets', waited for by many clinicians. The use of monoclonal antibodies against the escape mechanisms of tumours can be a good auxiliary method. There are too little data on the value of antibodies directly targeting tumour cells and on combined passive immunotherapy. Due to constant research, other modalities, such as prodrug activation, T cell activation, the use of intrabodies, T bodies, and conjugated antibody fragments might also prove to be valuable.

Keywords: Lung cancer; Monoclonal antibodies; Anti-idiotype vaccines; Immunotoxins; (Radio)Immunoconjugates; Prodrug activation; T cell activation; Intrabodies; T bodies; Radioimmunoguided surgery; Immunoguided focal ablation

Introduction

It seems that the conventional therapy of lung cancer (surgery, chemotherapy, radiotherapy) has reached a therapeutic plateau. The constant attempts to further improve their efficacy in survival, symptom control and quality of life have brought no real success yet. Moreover it is known that chemo-, and radiotherapy are neither specific, nor selective but are associated with significant adverse events and toxicity, and surgery has its morbidity too. The search for new therapeutic strategies is understandable.

The therapeutic application of antibodies against tumours is a longstanding desire. The target molecules of antitumour antibodies are the tumour associated antigens (TAAs), that are called lung cancer associated antigens (LCAAs) in the case of lung cancer. Data on the various known LCAAs and the numerous antibodies generated against them were collected and grouped by international workshops.[1] Research, aiming to recognize still more LCAAs and antibodies against them has not stopped.

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The invention of hybridoma technology which allowed the production of monoclonal antibodies (mAbs) in large amounts was a cornerstone in research. Early investigations clarified some basic data and raised some problems on the use of mAbs in therapy of diseases. One issue that had been a fear earlier, the possible dangerous cross-reactivity of the mAbs with normal tissues, has luckily not been verified by trials. Another, still existing problem is associated with that most therapeutic antibodies are still produced by mouse cells. If we apply these antibodies in humans, however, T cells, and human anti-mouse antibodies (HAMAs) are generated against them.[2,3] Attempts for the blocking of this human antimouse response resulted in changing the stems of the murine immunoglobulin molecules to human with genetic methods. The first chimeras contained about 30% mouse part, but further cutting the mouse component down to 5–10%, 'humanized' chimeric antibodies were produced. It is agreed, that human monoclonals could solve finally the immunoreaction problem, however, because of technical difficulties, very few human antibodies have been tested yet.[4] Parallel with the development of human antibodies by the way, there are also attempts for making advantage out of the murine part of the chimeric antibodies. Namely, the murine part is used for triggering host immune responses to destroy the whole antibodies, together with the bound tumour cells.[5]

A guideline of the American Medical Association for monoclonal antibody nomenclature proposes that all monoclonal antibody names should end with the suffix 'mab', indicating 'monoclonal antibody'. The name of an antibody from a mouse source should add the letter 'o' to the suffix to become 'omab'. For a chimeric antibody, the name should add the letters 'xi' to the suffix to become 'ximab' as in cetuximab. The name for a humanized antibody should add the letters 'zu' to the suffix to become 'zumab', as in trastuzumab, or bevicizumab.[6]

The application of mAbs in the therapy of lung cancer can be grouped as in Table 1.

Table 1
The application of mAbs in the therapy of lung cancer

Passive immunotherapy with mAbs	mAbs directly targeting tumour cells
	mAbs targeting tumour growth- and proliferative factors
	mAbs targeting the escape mechanisms of tumour cells
	Combined passive immunotherapy with mAbs
Active immunotherapy with mAbs	Anti-idiotype method
Antibody targeting with immunoconjugates	Immunotoxins
	Radio-immunoconjugates
	Chemo-immunoconjugates
The use of mAbs against tumours in other, early phase applications	Prodrug activation
	T cell activation
	Redirection of T cells with T bodies
	Intrabodies
	Antibody fragments
MAbs in surgery and in other ablative methods	Radioimmuno-guided surgery
	Immunoguided ablation techniques

Passive immunotherapy with monoclonal antibodies

Monoclonal antibodies directly targeting tumour cells

Mechanism

In this approach the tumour cells are attacked directly by the monoclonals. After fixation to tumour cells, activation of the complement cascade (complement dependent citotoxicity), or the activation of certain effector cells happens (antibody dependent cell mediated citotoxicity), both of which results in tumour cell death.[7] Some catalytic antibodies ('abzymes') follow, however, another pathway, they show direct citotoxicity, by the lysis of certain chemical bonds in the tumour cell membrane.[8]

Ways of research

An interesting phenomenon of antigenic modulation, which involves internalisation, or sloughing of the antigens in response to binding by the antibodies can cause a decrease of the number of antibodies on the tumour cell surfaces to below the threshold required for citotoxicity. Thus, search is directed for non-modulating tumour associated antigens as targets for antibodies. Further research is also needed for the better knowledge of the abovementioned abzymes as well.

Summarized opinion on the use of mAbs directly targeting tumour cells

Although it seems to be the simplest and most obvious therapeutic mode of action, there are still more data available on the details of the technique than on clinical trials, concerning either pulmonary-, or other type of malignancies.

Monoclonal antibodies targeting tumour growth- and proliferative factors

Phase of research

At the moment, this field of antitumour mAb therapy is the most widely investigated one, where research has