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Surveying the role of immunology in advancing anticancer therapy

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1. Introduction

Although tumour immunology has been the subject of research and clinical investigation for several decades, there has undoubtedly been a resurgence of interest within recent years in the immune response to cancer, not only as a basis for new therapies, but also as a critical element in realising the immense promise of modern anticancer drug development, which has been focused particularly on targeted therapy with small molecules.

Viewed from a certain perspective, the future for cancer therapy appears very bright indeed. The armamentarium looks set to expand at an unprecedented rate over the next 5 years, as a wide range of small molecules currently in development is introduced into clinical practice (Fig. 1). The reality could be rather different, however, since the hurdles in taking a drug to the clinic can be substantial, and much depends on whether society will be willing to meet the cost, a question that will depend in turn on how effective the new drugs turn out to be.

In practice cancer drug development will need to be prioritised at a relatively early stage if drug developers are to manage the difficult balance between investment and return and to introduce effective treatments that health providers will consider economic. How can such prioritisation be achieved? How will diagnostics services be provided to identify patients likely to respond to targeted therapy? Can valid surrogate endpoints be established in cancer to make novel drug development sufficiently cost effective? Can we use healthy volunteers in first to man studies of cancer drugs? Immunology can provide an answer to many of these questions.

2. Immunology in drug development

There are essentially only four approaches for industry to pursue in developing novel therapies for cancer: small molecules, monoclonal antibodies, gene therapy, and vaccines (Fig. 2). In recent years, the energy of industry has been concentrated on developing small molecules, but since the introduction of trastuzmab in 1999, and later of rituximab and bevacizumab, monoclonal antibodies have been a resounding and surprising success. As a result, drug developers are looking much more closely at tumour immunology in all its aspects, to investigate whether in its broad sense it can help in the development of small molecules and be combined with small molecules in the adjuvant setting, which is clearly the direction in which molecular therapies are headed.

The way clinical research and development is organised is going to be heavily dependent on immunology as an analytical tool in the coming years. Drug developers are going to be unwilling in the future to pursue clinical trials unless a bio-

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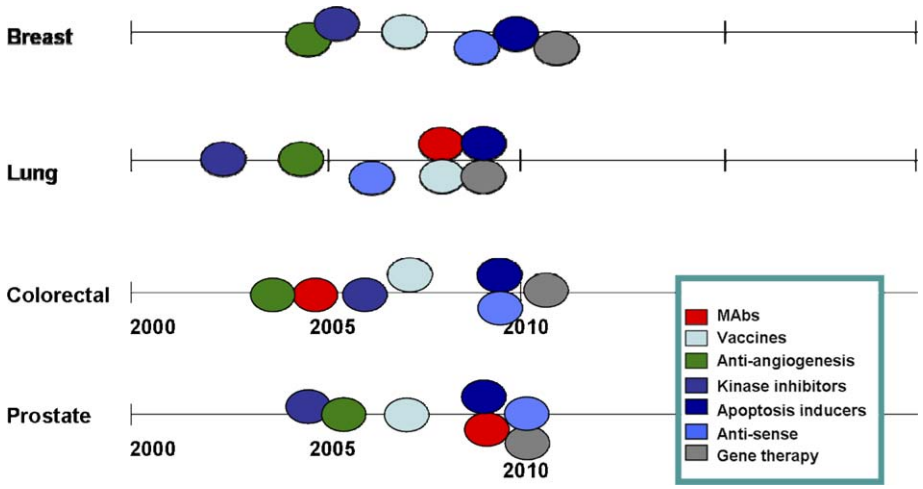

Fig. 1 – A considerable number and variety of novel therapies for cancer are potentially going to become available within the next few years, as illustrated by these data on predicted approval dates (New Drug Applications; NDAs) for new cancer therapies in the USA. Reprinted with permission from Ref. [2].

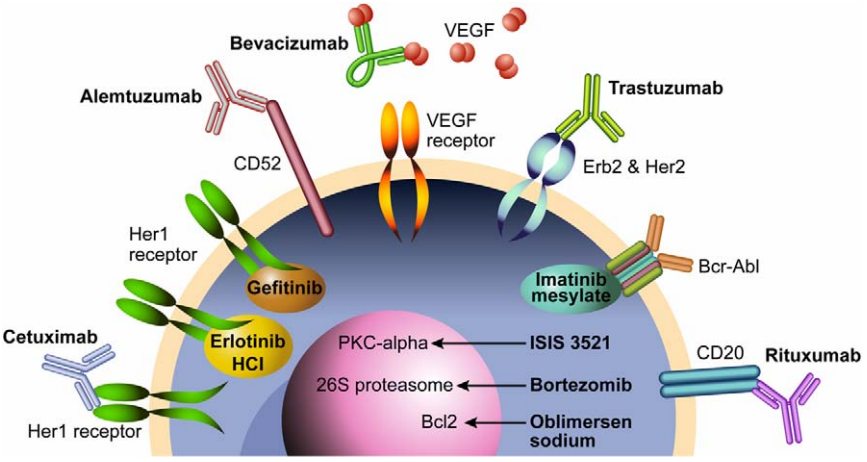

Fig. 2 – New therapeutic strategies in oncology include targeting cell signalling pathways implicated in tumour differentiation and growth, through small molecule tyrosine kinase inhibitors, and monoclonal antibodies. PKC, protein kinase C; VEGF, vascular endothelial growth factor.

marker of response is available. Here there is a parallel with the role of cholesterol as a biomarker for the efficacy of statins in reducing cardiovascular risk.[1]

Although at present no such markers exist for cancer, immunological techniques can almost certainly be used to provide them. They will enable the development of a clinical assay based on a drug's molecular target, which could be used to look for molecular signatures of response in different subsets of patients, and for markers of downstream biochemical changes. Such clinical assays would mean that rather than concentrating on toxicity, Phase I clinical trials could be used to determine maximal effective dose,[2] so streamlining the discovery process.

Another development I consider likely will be the need for a surrogate for short-term responses in Phase III clinical trials, in order to allow patients who fail to respond to be discontinued from the trial, again helping to streamline and manage the costs and practical challenges of drug development, as well as allowing non-responders to be identified early and so be in a position to receive an alternative treatment.

The importance of biomarkers and surrogates in modern cancer drug development was powerfully illustrated in the case of the tyrosine kinase inhibitor, gefitinib. Clinical trials in small numbers of patients with metastatic lung cancer suggested a dramatic response to treatment.[3,4] Subsequent Phase III trials, however, failed to demonstrate any difference between gefitinib and best available chemotherapy.[5] This was obviously a tremendous disappointment for patients with lung cancer, and it also raised serious issues for the development of new drugs, which is driven by commercial imperatives as well as by scientific aspirations, and which therefore depends on a certain degree of predictability.

Not surprisingly, experiences such as that with gefitinib have led to strenuous efforts to incorporate techniques into drug development that can help to segregate responders from non-responders in advance of large clinical trials. And it is

from immunology that such techniques are being derived. Automated, quantitative immunohistochemistry based on sophisticated tissue analysis now enables individual response to be assessed objectively and reproducibly, avoiding the practical limitations of relying on histopathologists, who are often in short supply.

3. Immunology and cancer therapy

Immunotherapy for cancer is developing through a range of approaches, including targeting with monoclonal antibodies, either alone or coupled to a drug, toxin or radioisotope, the use of recombinant cytokines, and specific immunotherapy through activated T cells.

As I mentioned above, one of the developments that has placed immunology at the centre of clinical research in oncology in recent years is the introduction of monoclonal antibodies as targeted therapy. And if metastatic disease is the setting in which these agents were first shown to be effective, it is in adjuvant therapy that their benefits will be fully realised. Based on the theoretical understanding of how these drugs act, a monoclonal antibody would be expected to have a much more marked effect in the adjuvant setting.

Recently the results from two large clinical trials comparing adjuvant treatment for breast cancer with and without trastuzumab have demonstrated that trastuzumab confers a significant benefit in terms of disease-free and overall survival compared with chemotherapy alone (Fig. 3).[6,7] These are powerful data, and I would expect similarly dramatic results to be seen with adjuvant bevacizumab.

Inducing a T cell-mediated response to a tumour-specific antigen is now recognised as a rational approach to cancer therapy, and a range of potential therapeutic target antigens is being explored (Table 1). Advances in developing immunotherapy via T cell activation are likely to arise from techniques that can purify the peptide antigen and so standardize the immunogen for use across the patient population. A diagnostic assay could be used to determine whether an individual's tumour did indeed express the antigen, and therefore whether that patient would be likely to respond. Antigen presentation is a critical factor in immunization, and this can be enhanced by the use of dendritic cell precursors, which are isolated from the individual and allowed to take up antigen before being incubated and then infused back into the patient, where they

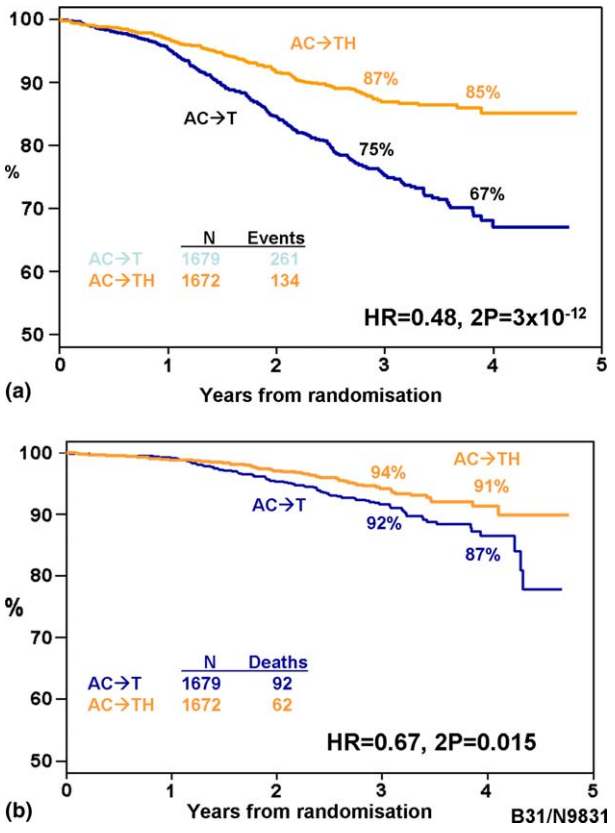

Fig. 3 – The combined analysis of NCCTG-N9831/NSABP-B-31 demonstrated that the addition of trastuzumab to AC paclitaxel significantly improved disease-free survival (a) and overall survival (b) in women with HER2-positive breast cancer. (A, doxorubicin; C, cyclophosphamide; T, paclitaxel; H, trastuzumab).

can generate a cytotoxic T cell response directed at the antigen and hence at the tumour.

3.1. *Immunology and cancer prevention*

Another area in which immunology is likely to play an increasingly important role is cancer prevention in individuals considered to be at increased risk for disease. There is currently intense interest in identifying genetic polymorphisms

Table 1 – Potential therapeutic target antigens

Differentiation antigens	Shared self-antigens	Mutated self-antigens	Overexpressed oncopeptides
Tyrosinase	MAGE 1	CDK4	HER2/Neu
CEA	MAGE 3	BCatenin	P53/WT
Ig idiotype	BAGE	P53	
GP100	RAGE	Ras	
GP75	MUC 1	Bcr-abl	
TRP2	NY-ESO1		
PSA			

BAGE, B melanoma antigens; CDK, cyclin-dependent kinase; CEA, carcinoembryonic antigen; MAGE, melanoma antigen; MUC1, human mucin 1 protein; RAGE, receptor for advanced glycation end-products; PSA, prostate-specific antigen; TRP, tyrosinase-related protein-2; WT, wild type.

associated with increased cancer risk; not mutations in genes such as BRCA1, BRCA2 and APC (adenomatous polyposis coli), which are associated with a markedly increased risk for cancer, but those in low penetrance susceptibility genes, which are associated with a less marked increase in cancer risk on their own but which when pooled together can indicate groups of people in which cancer incidence is likely to be high. Over the next decade, molecular epidemiology will enable genetic and environmental factors to be clearly related to one another, allowing individual risk to be identified more precisely. While we already have markers of cancer risk, these are not molecular but histopathologic. So for example there is prostatic intraepithelial neoplasia, hyperplasias in the breast, dysplasias in the lung, adenomas in the colon, and so on. These are not good markers for drug development because they require biopsies and subjective assessment by a pathologist, rather than objective scoring of a biochemical or molecular factors. So I think we are going to see a huge level of interest in this area with immunology playing a large part in the diagnostics.

4. Summary

There are a number of obstacles to overcome in harnessing the immune response for use in cancer therapy. In the immunological targeting of cancer the cost of development is a major obstacle, especially if therapies have to be tailored to individual patients. Another challenge is the lack of surrogate endpoints for response. There are good surrogates in immunotherapy for immune stimulation, but correlating these to outcomes in terms of clinical gain is difficult. We need better immune adjuvants, particularly to obviate the need to work with cells ex vivo, which currently adds to the complexity and the cost of treatment. And then there is the sheer complexity of cancer management resulting from aspects such as immunosuppression, the generation of antigen loss variants, and the considerable heterogeneity of tumours between, and even within patients, which presents subtle molecular and immunological differences that make a uniform approach very difficult.

Despite these challenges I believe that over the next decade, immunology is going to play a prominent part in the effort to reduce the burden of malignant disease, not just as a basis for new therapies exploiting the immune response, but also as a means of addressing some of the challenges inherent in introducing molecular targeted small molecules and in new approaches to classical chemotherapy.

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