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REVIEW PAPER

Therapeutic strategies with monoclonal antibodies and immunoconjugates

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CONTENTS

Introduction

Monoclonal antibodies (mAbs) are emerging as a major modality for both detection and therapy of various pathological conditions, including malignant disease. Murine monoclonal antibodies have been developed which react with tumour-associated antigens expressed on or near the cell surface, and present in high concentration on malignant tissues but in minimal amounts on normal tissues (Boyer *et al.*, 1988). These include mAbs against colon cancer, ovarian cancer, breast cancer and neurological tumours, which have been used therapeutically either alone or conjugated to cytotoxic agents (Baldwin & Byers, 1987) and diagnostically coupled to radioisotopes for gamma camera imaging of patients (Chatal, 1988, Pimm, 1987). More recently investigators have taken advantage of the well-defined antigens on the surface of lymphoid cells, and mAbs directed against such antigens have been used therapeutically against lymphoid malignancies and autoimmune diseases, including prevention of renal allograft rejection and treatment of graft-versus-host (GVH) disease (Goldstein *et al.*, 1985; Byers, 1987; Byers *et al.*, 1987a; Fahey *et al.*, 1987; Youle & Colombatti, 1986).

In spite of the encouraging clinical results, including the use of the anti-T-cell receptor mAb OKT3 in renal allograft rejection (Goldstein *et al.*, 1985; Mayes *et al.*, 1988), the central limitation in using these murine products has been the generation of an immune response to murine immunoglobulin which usually precludes retreatment. Especially in solid tumour therapy, retreatment is viewed as a key factor in allowing this therapeutic modality to be optimized, and a variety of approaches to solve the problem are underway.

These issues are reviewed in relation to the now quite extensive advances in designing immunoconjugates for therapy, particularly in malignant disease.

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Therapeutic use of mAbs

Murine monoclonal antibodies that recognize tumour-associated antigens and localize in tumours, or that have well-defined reactivity against antigens on lymphocytes, are being evaluated for therapy (Baldwin & Byers, 1987). Unmodified antibodies have demonstrated efficacy in some cases. For example, in renal allograft transplantation OKT3 antibody directed against the T-cell receptor has been proven quite effective in reversing rejection, probably as a result of blocking lymphocyte–antigen interactions (Goldstein *et al.*, 1985). Also, unconjugated antibodies are being used in cancers such as colon cancer (LoBuglio *et al.*, 1986; Sears *et al.*, 1985) and neuroblastoma (Cheung *et al.*, 1987). The rationale for their use is that host defence mechanisms such as antibody-dependent cell cytotoxicity (ADCC) can serve as the cytotoxic modality, but consideration is now being given to the view that murine monoclonal antibodies may be inducing anti-idiotypic antibodies that will react against the tumour (Viale *et al.*, 1987; Nepom & Hellstrom, 1987; Herlyn *et al.*, 1987a, b). These approaches have shown some encouraging results—for example in the case of antibodies against neuroblastoma—but most attention has turned to the use of mAbs for targeted therapy using cytotoxic agents, including radioisotopes and toxins.

The initial selection of antibody for use as a targeting agent is primarily based upon its reactivity with appropriate target cells in comparison with binding to normal cells, since this latter reactivity will be translated *in vivo* into 'side-effects'. This is still a major limitation, although there are only a few antibodies which meet specificity requirements. For example, with solid tumours, preclinical studies indicate that antibodies which react with malignant melanoma (Spitler *et al.*, 1987) and colorectal cancer (Baldwin & Byers, 1988; Byers *et al.*, 1988a, b) had minimal normal tissue reactivity, and immunotoxins made from these monoclonal antibodies were well tolerated in clinical studies. However, other potentially useful antibodies, such as

those binding to epidermal growth factor receptor (Griffin *et al.*, 1987; FitzGerald *et al.*, 1987) and to breast/ovarian cancer-associated mucins (Price, 1988a, b), exhibit quite widespread normal tissue reactivity. Immunotoxins constructed with these antibodies may exhibit normal tissue toxicity, thus limiting their clinical use.

The mechanism of action of the different cytotoxic agents influences to some extent the choice of antibody. With radioisotopes, the monoclonal antibody must be targeted to the tumour, but internalization into the cell may be detrimental since it can result in deconjugation of the isotopes from the monoclonal antibody, and exocytosis, facilitating its removal from the tumour (Press *et al.*, 1988). On the other hand, most cytotoxic drugs, e.g. methotrexate, are bound to the antibody by labile bonds and endocytosis into an acidic intracellular compartment maximizes activity through drug release (Garnett *et al.*, 1985; Embleton & Garnett, 1986). Antibody targeting with these agents is intended primarily to reduce uptake by normal tissues, so lowering toxicity, although it may convert resistant cells to susceptible cells in cases where resistance is due to defective drug uptake. In contrast, ricin toxin A chain (RTA) is inactive extracellularly and non-toxic as the free agent. Antibody conjugation targets the toxin moiety to the target cell, allowing it to be internalized by endocytosis (Baldwin *et al.*, 1988; Byers *et al.*, 1988a).

Immunotoxins

Toxins of plant and bacterial origin represent a class of highly cytotoxic agents for linking to monoclonal antibodies to form immunotoxins (Vitetta *et al.*, 1987; Baldwin & Byers, 1987; Blakey & Thorpe, 1987). One type of toxin, typified by ricin produced from beans of the plant *Ricinus Communis*, is composed of two disulphide-linked subunits. The intact toxin binds to mammalian cells through galactose residues on the B subunit and is endocytosed (Van Deurs *et al.*, 1988). The A chain, which is inactive extracellularly, after introduction into the cell catalytically inactivates the 60s ribosomal subunit of eukaryotic cells by modifying one or two nucleoside residues of the 28s ribosomal RNA (Endo *et al.*, 1987). If the bond between the A and B chains is broken and an antibody substituted for the B chain, the A chain can now be directed to specific target cells. This approach has now been used for several A–B chain toxins, including pseudomonas exotoxin, diphtheria toxin and abrin (Vitetta *et al.*, 1987; Baldwin & Byers, 1987).

Much work has been done with RTA immunotoxins containing ricin A chain conjugated to antibody through the cross-linker *N*-succinimidyl-3-(2-pyridyldithio) propionate (SPDP). This contains a disulphide bond, and it is generally assumed that this is cleaved intracellularly to allow the A chain to translocate through the cytoplasm to the Golgi apparatus. The pharmacokinetics of the clearance of the antibody moiety of the immunotoxins is markedly changed by the addition of the RTA (Byers *et al.*, 1987b; Bourrie *et al.*, 1986; Blakey *et al.*, 1987) since this protein contains mannose-terminating oligosaccharides that are recognized by reticuloendothelial cells, including Kupffer cells in the liver (Blakey *et al.*, 1987). This results in rapid liver clearance and reduces the blood half-life from days to hours. Increasing the blood half-life improves localization of immunotoxin in the tumours, so various strategies are being devised to eliminate the mannose residues on the RTA without affecting activity. These include deglycosylation of RTA (Blakey *et al.*, 1988), synthesis of recombinant RTA, and use of a subfraction of RTA with reduced oligosaccharide content (Fulton *et al.*, 1986). The increased circulation time increases localization at the disease site; this must be balanced against the possibility of increased or altered toxicity.

Endocytosis and intracellular processing are essential for immunotoxins to exert their effect (Vitetta *et al.*, 1987; Baldwin *et al.*, 1988). Since the mechanism of intracellular trafficking is poorly understood, immunotoxins are selected by screening them for specific cytotoxicity. This is usually expressed as the concentration of immunotoxin necessary to inhibit 50% of target cell growth *in vitro* (IC_{50}) and, in most cases, the difference in potency between immunotoxin and free RTA is in the order of 10^3–10^4-fold. One immunotoxin against the CD22 antigen on B lymphomas actually has a lower IC_{50} than whole ricin (May *et al.*, 1986).

As additional information of the mechanism of internalization and intracellular trafficking of immunotoxins is obtained, construction of potent immunotoxins should become more efficient. Both the rate of endocytosis and the intracellular compartment into which the immunotoxin is moved depends in some part on the antigen to which the monoclonal antibody binds. Receptor-mediated endocytosis is more efficient than pinocytosis, for example the rate of endocytosis of a gelonin-containing immunotoxin which reacts with the C3b receptor on human B lymphocytes can be markedly increased by infection with Epstein–Barr virus, which is the preferred ligand for the receptor (Tedder *et al.*, 1986). Also, recent studies by Sandvig *et al.* (1987) demonstrated that under conditions in which receptor-mediated endocytosis through coated pits is blocked, internalization of transferrin and epidermal growth factor does not occur, but internalization and intoxication by ricin continues essentially unhindered. These and other data have been taken to suggest that at least two independent mechanisms exist for the internalization of surface-bound ligands, one via coated pits, and the other via 'smooth' pits which lack a clathrin coat. This may influence the cellular compartment into which the immunotoxin is directed. After endocytosis, the endocytotic vacuole is acidified and, in contrast to chemoimmunoconjugates and immunotoxins such as diphtheria toxin, RTA immunotoxins are inactivated by acidic environments. Thus for these conjugates, any inhibition of intracellular acidification increases activity. The potent potentiating agents for many immunotoxins, monensin and ammonium chloride, are postulated to work by decreasing the rate of intracellular acidification, thereby prolonging intracellular activity of the immunotoxins.

Chemo-immunoconjugates

The design of chemo-immunoconjugates is developing along similar lines to those established with immunotoxins, and conjugates have been produced with several classes of cytotoxic drugs, including alkylating agents and antimetabolites (Baldwin, 1985; Baldwin *et al.*, 1986; Ghose & Blair, 1987). These are produced by conjugating drug to antibody through a specific functional group such as amino, hydroxyl or sulphydryl residues. In this case, the selected conjugation site should not be required for drug action or, if so, should become available following intracellular release of the drug. Cytotoxic drugs are generally less active than toxins and it is necessary to introduce the maximum number of drug residues compatible with retention of antibody reactivity. High drug substitution ratios have

been reported, but with monoclonal antibodies of the IgG subclass, substitution of more than 10 drug residues per antibody molecule may produce an unacceptable level of antibody damage. Consequently drug carrier molecules such as human serum albumin and dextrans are being used to yield antibody conjugates with much higher molar ratios of drug to antibody (Garnett & Baldwin, 1986; Endo *et al.*, 1988). Conjugates of large molecular size may have inappropriate pharmacokinetic properties and are less able to penetrate tumour tissue. Currently, therefore, attention is being given to the chemistry of drug–antibody conjugation so as to improve the potency of chemo-immunoconjugates. This includes the selection of more cytotoxic analogues of the drugs used for antibody conjugation, and design of new drug carrier molecules to replace currently used polymers, as well as modification of the drug conjugates, particularly the overall charge in relation to their pharmacokinetics.

The use of hybrid antibodies is being considered as an alternative to chemical conjugation for *in vivo* targeting drugs to tumours. Hybrid–hybrid monoclonal antibodies recognizing both a tumour-associated antigen and the drugs are being produced either by fusion of two existing hybridomas or by fusion of one existing hybridoma with spleen cells from donor mice immunized against the other antigen. Studies in this field have been reported by Corvalan *et al.* (1987a, b) in which a hybrid antibody reactive with a carcinoembryonic antigen (CEA) epitope and vinca alkaloid was produced by fusion of an anti-CEA antibody-producing hybridoma with spleen cells from mice immunized with vindesine–protein conjugate. The IgG antibody had the γ1 heavy chain from the parental anti-CEA antibody and a γ2a from the anti-vinca alkaloid donor lymphocyte. This antibody localized in an appropriate CEA producing colon carcinoma xenograft. The antibody also induced profound changes in the biodistribution of ^{3}H-labelled vinblastine, resulting in specific localization of the drug to tumour tissue and so producing a therapeutic response.

It is feasible to prepare monoclonal antibodies to other drugs and therefore there is the possibility of constructing a range of hybrid antibodies. For example, Pimm *et al.*, (1987) with a hybridoma producing monoclonal antibody to methotrexate showed that complexing antibody with drug profoundly altered the biodistribution of the drug, prolonging blood survival and reducing liver uptake, and clearly hybridomas such as this are candidates for constructing hybrid–hybrid antibodies with anti-tumour antibodies.

Clinical trials

Clinical trials are in progress with murine monoclonal antibodies alone and as immunoconjugates. Antibodies specific for the idiotype of the surface immunoglobulin of B-cell lymphomas have been used successfully in inducing tumour regression, but the clinical outcome has been widely variable ranging from prolonged remission to no effect (Lowder *et al.*, 1987). Factors involved include antigen modulation, which may be of particular concern with lymphoid tumours, and generation of anti-mouse antibody responses which markedly alter antibody pharmacokinetics. Another approach with B-cell tumours involves treatment with murine monoclonal antibodies directed against normal CD20 antigens. Treatment of four patients with [illegible] produced a 90% elimination of malignant cells from the blood in two patients and a reduction in lymph node disease in one patient, but the duration of remission was shortlasting (Press *et al.*, 1987). Antibodies specific for tumour-associated gangliosides which activate human complement and are active in ADCC are in clinical trials with neuroblastoma (Cheung *et al.*, 1987). The antigen recognized by this antibody is also expressed on neurons and peripheral brain fibres. Because of pain during infusion, patients must be anaesthetized and maintained on analgesics for several weeks afterwards. However, complete remission of two neuroblastomas have been reported, suggesting that, with appropriate medical support, substantial reactivity with normal tissues can be tolerated.

The most successful therapeutic use of an unconjugated antibody has been the use of OKT3 in renal allograft rejection (Goldstein *et al.*, 1985). This murine monoclonal antibody is directed against the CD3 (T-cell receptor) antigen on mature human T cells and blocks their function. When given over a 14-day period as initial therapy in patients experiencing acute rejection, it will reverse 94% of the rejections, and significantly improve 1 year graft survival to 62%. This is now an approved drug for that indication.

Clinical evaluation of radioisotope-labelled monoclonal antibodies is in progress, using 131-iodine (gamma and B emission), 90-yttrium (gamma emission) and 211-astadine (α-emission) (Humm, 1986; Order *et al.*, 1988; Sands, 1988). It has been argued that the minimum requirement for effective therapy using radioimmunoconjugates is accumulation of 10 times more conjugate in tumour compared with blood (Vaughan *et al.*, 1987) and this cannot be attained by intravenous administration. Therefore, recent clinical applications have focused upon intraperitoneal injection of 131-iodine-labelled antibody in patients with ovarian and colon cancer and intrathecal injection in patients with malignant melanoma. In one trial in ovarian cancer (Stewart *et al.*, 1988) patients were treated with a range of antibodies. There were complete responses in 3/6 patients with microscopic disease and partial response in 2/15 patients with nodules smaller than 2 cm.

The most impressive response to immunotoxin therapy so far has been in the treatment of acute graft versus host (GVH) disease developing following bone marrow transplantation (Kernan *et al.*, 1988; Byers *et al.*, 1987b). The immunotoxin used contains RTA conjugated to a monoclonal antibody reacting with the CD5 antigen on mature T lymphocytes. In 12/25 evaluable patients, progression of disease was reversed after the first seven doses of immunotoxin; in another five it was stabilized. Overall these patients continued to attain complete responses as late as 60 days after therapy, whereas most of the non-responders had died by Day 40. Responses were seen in all three involved organs, skin, gut and liver. Pharmacokinetic studies indicated that the immunotoxin was cleared rapidly from blood. Even so, the circulating T lymphocytes, as measured by CD3 and CD5 expression, dropped by Day 6 of treatment to less than 20% of the initial value and remained low for several weeks to months thereafter.

Clinical trials with ricin A chain immunotoxins also include phase I/II trials in malignant melanoma with antibody directed against the high molecular weight (>200,000) melanoma antigen (Spitler *et al.*, 1987) and a phase I trial in colorectal carcinoma with monoclonal antibody 791T/36 which reacts

(gp72) (Byers *et al.*, 1988b). These immunotoxins are well tolerated in terms of side-effects. These include reversible hypoalbuminemia, and myalgias, which are generic for the immunotoxins, and proteinuria which is associated with the immunotoxin constructed with monoclonal antibody 791T/36. In the melanoma study, approximately 50% of the patients showed some degree of response, with one patient having complete remission. In the colorectal cancer study, three patients with hepatic metastases had resolution of the smaller lesions. Although encouraging, most of the clinical responses have not yet reached the requirement for categorization as response by the WHO criteria. For this to be achieved it is likely that retreatment schedules will be necessary and for this the development of anti-mouse antibody responses in immunotoxin patients must be controlled.

Human anti-murine monoclonal antibody responses (HAMA)

Clinical impact

Almost all of the murine monoclonal antibodies being used clinically provoke antibody responses (HAMA) in patients. These include antibody responses against the framework, the isotype, and the idiotype of the murine IgG antibodies. It is rare that anaphylaxis or serum sickness occurs in patients with HAMA when retreated with mAb, although anaphylactoid reactions are not uncommon and primarily consist of periorbital oedema or urticaria. But HAMA responses lead to altered pharmacokinetics of the injected monoclonal antibody. Anti-melanoma immunotoxin is rapidly cleared from serum with reduced drug levels being attained (LoBuglio *et al.*, 1988a). Immunoscintigraphy of tumours with radiolabelled antibody is also seriously compromised in patients developing HAMA, and has resulted in negative imaging of tumour with radiolabelled product (immune complexes) being localized in liver and spleen (Pimm *et al.*, 1985; Perkins, Pimm & Powell, 1988). The extent to which HAMA influences therapy clinically is still unclear. One study of patients treated with OKT3 (Jaffres *et al.*, 1986) reported that of 21 patients given OKT3 60% made anti-Id antibodies, which in some cases interfered with its therapeutic effectiveness, while another report indicated that low levels of blocking antibodies did not significantly compromise access to OKT3 for treatment of subsequent rejection episodes (Mayes *et al.*, 1988). Possibly the more important finding is the fact that even though these patients were immunosuppressed with azathioprine, prednisone, and in some cases cyclosporine, they still were able to generate HAMA with anti-Ids as a prominent feature of the response, even though this must constitute a relatively minor portion of the murine monoclonal antibody. The actual generation of HAMA will probably depend in some part on the underlying disease as well as the concomitant immunosuppression; for example patients with cutaneous T-cell lymphoma have a higher incidence of HAMA to the anti-CD5 mAb T101 than do patients with CLL, where almost no patients produce an immune response (Dillman *et al.*, 1984). Also, patients receiving an immunotoxin composed of an anti-CD5 mAb coupled to RTA, who are suffering from GVH disease and therefore are immunosuppressed both exogenously and endogenously, have very little HAMA (V. S. Byers, R. P. Mischak, N. Kernan and P. Scannon, unpublished findings). In some situations, a single course of mAb therapy may be sufficient to cyte globulin in which 4–10 days of therapy is sufficent to cure aplastic anaemia (Young *et al.*, 1988). Overall, however, most investigators take the position that if multiple courses of mAb are to be used therapeutically, reliable methods for abrogating the immune response must be devised.

Approaches to abrogate anti-mouse immunoglobulin responses in patients

Concomitant treatment with immunosuppressive medication is one method being developed, and in one study the primary HAMA response was blunted following pretreatment with azathioprine/prednisone for 8 weeks (LoBuglio *et al.*, 1988). A significant inhibition of the primary HAMA response has been achieved with cyclosporin (CsA) pretreatment for 6 days, although CsA had no effect on abrogation of response in patients with pre-existing anti-murine antibodies (Lederman *et al.*, 1988). The problems with such regimens is non-specific immunosuppression, and toxicity of the additional drugs which makes such therapy with mAbs more hazardous than with mAb given as a single agent. An alternative approach is to produce a human antibody or 'humanized' version of murine monoclonal antibodies.

Initially, intensive efforts were directed toward making human mAbs, but products generated have been unsatisfactory (Campbell *et al.*, 1987; James & Bell, 1987). Lymphocytes from human peripheral blood or from draining nodes from human tumours were fused with either human or murine myeloma partners, and the mAbs generated were of the IgM subclass and usually directed against intracellular antigens. IgM antibodies do not function well as imaging agents, probably because they are too large to marginate from the peripheral blood into the tissues, and would also be expected to be poor therapeutic agents for that same reason. The problem in finding mAbs directed against human cell membrane antigens may relate to humans being tolerant to such antigens, but the reason for the difficulty in producing human mAbs of the IgG subclass is still not understood. Meanwhile, however, methods are being devised by which the variable region of the murine mAb may be engineered onto a human constant region. A chimeric antibody composed of the variable regions of murine monoclonal antibody 17.1A (IgG2aK), which recognizes a glycoprotein present on human colorectal cells, has been coupled with the constant region of human IgG3. This chimeric 17.1A mAb has the same reactivity against colon tumour cells as the native antibody, and both have identical capacity to inhibit radiolabelled native 17.1A binding to tumour cells (Shaw *et al.*, 1987). Native 17.1A has been used extensively in clinical trials in colorectal cancer patients, and it elicits a very pronounced HAMA response, altering its pharmacokinetics (LoBuglio *et al.*, 1988b; Khazael *et al.*, 1988). In contrast, antibody responses have not been detected in patients receiving multiple treatments with the chimeric 17.1A, and the pharmacokinetics of the chimeric 17.1A was not modified, as additional evidence of lack of an antibody response (Shaw, Khazaeli & LoBuglio, 1988). This result was unexpected since this construct still has the whole of the variable region as murine derived, and since the idiotypic component of the immune response forms a prominent proportion of the HAMA response. Several groups are, therefore, in the process of 'humanizing' murine mAbs, using various techniques such as the chimeric antibody constructed from rat

able regions from the heavy- and light-chain domains into a human IgG1 molecule (Riechmann *et al.*, 1988). This chimera was as effective as the native mAb in complement-mediated lysis of B-cell lymphocytic leukaemia cells.

Control of the immune response to immunoconjugates will probably be more difficult, especially where the conjugated moiety itself is immunogenic, e.g. ricin A chain. The immunoconjugates themselves should theoretically exert a cytotoxic effect not only against their target cell, but also against the antigen-specific cells of the immune system that are capable of producing antibody responses against them. Thus antigen-specific B lymphocytes having clonally distributed specific surface immunoglobulin receptors should react with immunoconjugates. Such recognition should lead to endocytosis of the cytotoxic conjugate and, following intracellular release, the cytotoxic moiety should cause cell death. The HAMA seen with certain immunoconjugates, such as RTA-containing immunotoxins, indicates that for various reasons they fail to adequately exert a cytotoxic effect against B lymphocytes. Immunoconjugates have been constructed, however, which suppress anti-mouse antibody responses. Conjugates constructed with monoclonal antibody 791T/36 and cis-acontityl-substituted daunomycin render rats immunologically unresponsive to subsequent repeated immunization with the unconjugated antibody (Durrant *et al.*, 1988). However, rats still produced HAMA in response to challenge with the RTA immunotoxin made from 791T/36 antibody. This probably means that RTA itself is immunogenic and serves as an effective antigen-presenting molecule, possibly through its avid uptake by macrophages. Supporting this view is the finding that murine monoclonal antibody 791T/36 coupled to ricin A chain produces strong anti-idiotypic antibody responses in mice (Pimm, Durrant & Baldwin, 1988). Further manipulation may be necessary, therefore, to tolerize the host against the cytotoxic moieties such as ricin A chain prior to therapy with immunoconjugates constructed with humanized antibodies. Benjamin *et al.* (1988) showed that mice made tolerant to rat immunoglobulin constant region determinants were, in some instances, capable of inducing only minimal reactivity to the idiotypic region of the antibody and the same approach may be used to suppress specific responses to immunoconjugates. If, however, there is a non-specific enhancement of antigen processing by components attached to humanized murine monoclonal antibodies, the pathway would be to generate cytotoxic analogues to eliminate this component. For the moment, therefore, investigators using immunoconjugates continue to utilize concomitant therapy with immunosuppressive agents such as CsA.

Conclusions

One should not underestimate the complexities of the problems still to be resolved in producing monoclonal antibodies and immunoconjugates for clinical use, especially in solid tumours. Outstanding problems include improving the design of the immunoconjugates themselves, particularly refining techniques for directing the conjugation site away from the active site of the antibody and conjugating adequate amounts of cytotoxic agents. More effective conjugation procedures are also important, particularly with small hydrophobic molecules. Second generation immunoconjugates, one anticipates, will be pro-

Enhanced target tissue accessibility is very important with solid tumours, since these are notorious for poor vascularity. Longer serum half-life will increase tumour localization, but it probably will be necessary to develop agents with a direct effect on tumour vascularity for adequate penetration. Antigenic heterogeneity is also an issue that is being addressed by use of cocktails of monoclonal antibodies, and it is still under discussion as to whether the cytotoxic molecules bound to the different monoclonal antibodies should also be different. More important is the issue of antibody responses to the immunoconjugates. If these agents are viewed by the same criteria as conventional cytotoxic agents, it will be critical to retreat patients with more than one course of immunoconjugate, and possibly with immunoconjugates of different specificities. The antibody response seen with almost all monoclonal antibodies and immunoconjugates at present effectively restricts treatment to a single short cycle. Several strategies have been identified to overcome this, including the design of human or humanized monoclonal antibodies. Whether or not this will restrict the generation of anti-idiotypic antibodies is not yet known, although studies with monoclonal antibody 17-1A suggest that in some cases this may be achieved. Even so it seems that immunoconjugates may still produce anti-idiotypic antibodies, and so in these cases immunosuppressive procedures may be needed. This may be achieved with immunosuppressive drug treatment, but with the associated toxicities, particularly in treatment with cytotoxic immunoconjugates as envisaged in cancer patients, this is not desirable. An alternative approach is to devise methods for specific abrogation of antibody responses along the lines already reported with daunomycin–antibody conjugates or by some other form of immune intervention.

Considerable advances are being made in the clinical use of monoclonal antibodies and immunoconjugates. These include immunoscintigraphy with radioisotope-labelled antibodies for tumour detection, and monoclonal antibodies can be viewed as a new class of immunosuppressive agents in transplantation. Promising results are also being obtained in solid tumour therapy with immunoconjugates and one anticipates that this approach to cancer treatment will be even more effective with improvements in conjugate design.

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