Role of antibody therapy in lymphoid malignancies

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Introduction: Over the past decade, the potential for delivering targeted therapy against malignant disease by the use of monoclonal antibodies (MoAbs) has begun to be realized. The development of human or chimeric antibodies and protein engineering to combine MoAbs with other biologically active molecules, such as radio-isotopes, toxins, chemotherapy and cytokines, has made available a new range of agents with clinical activity.

Discussion: This article will review the requirements and strategies for successful MoAb therapy and the clinical experience in a range of lymphoid malignancies. On the basis of substantial experience of antibodies, such as rituximab and alemtuzumab, as single agents, there is now evidence from randomized trials that the addition of antibodies to chemotherapy improves efficacy and prolongs progression free and overall survival for patients with follicular and diffuse large B-cell lymphomas.

Conclusion: The trials of the next decade will address issues such as the optimal strategies and timing for clinical use, the role of radio- and immuno-conjugates and, finally, what other potential molecules, such as those influencing cell growth and death, may be targeted.

Keywords: monoclonal antibodies·lymphoma·leukaemia·radio–immunotherapy·rituximab·alemtuzumab

Introduction

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Many patients with lymphoid malignancies will not be cured by conventional chemotherapy. The main obstacles to achieving cure are the development of tumour resistance to chemotherapy and the dose-limiting toxicity of most drugs. Research has, therefore, focused on the development of targeted therapies that are more effective in overcoming resistance and are less toxic to normal tissues. The advent of monoclonal antibody (MoAb) technology in the 1970s[1] and the development of genetically engineered derivatives in the 1980s[2] have made possible the routine production of large quantities of MoAbs for the treatment of haematological cancers. In some of these diseases, MoAbs have now

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found a defined therapeutic role, whereas in others, evidence from clinical trials is still accruing.

Requirements for effective therapy with MoAbs

A number of factors appear to be important in the process between delivery of an MoAb and the death of the targeted malignant cell *in vivo*.

Properties of the tumour cell

The selection of the target antigen is clearly important. Ideally, therapeutic antibodies should be able to induce tumour cell death without damaging normal cells. Most MoAbs are not strictly tumour-specific, but are directed against lineage-associated cell surface antigens expressed on both normal and malignant cells. These MoAbs can therefore be used in a number of different malignancies, but have the disadvantage of causing a transient reduction in normal cells. In the case of haemopoietic malignancies, provided the stem cells remain unaffected, regeneration of normal cell populations can be expected. Unconjugated antibodies rely on their ability to induce host effector mechanisms that mediate cell death. The antigen site density and expression on the target cell need to be sufficient to activate these mechanisms. It is also important for these antibodies that the target antigen is neither shed nor internalized (antigenic modulation), which would make it inaccessible to the antibody and render the cell resistant to therapy. Sensitivity of different cell lineages both *in vitro* and *in vivo* varies significantly, despite the expression of comparable amounts of antigen.

Properties of the antibody

The properties of the MoAb itself play a role in determining the success of therapy. Certain antibody isotypes (e.g. IgG 1 or IgG 3) are known to have greater activity than others.

MoAbs need to be delivered efficiently to all tumour sites without being bound and cleared by free antigen in the serum. The accessibility of the tumour cells to the MoAbs is also an important factor. Antibodies are large molecules that may not penetrate deep into tissues, especially those that are poorly vascularized.

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In the past, most MoAbs were of murine origin and this foreign protein elicited an anti-globulin response. The human anti-mouse antibodies (HAMAs) neutralize the therapeutic MoAbs, thus limiting the clinical efficacy. This problem has largely been overcome by the introduction of less immunogenic chimeric and humanized antibodies, constructed by fusing the variable regions of murine MoAbs with normal human immunoglobulin genes,[2] which do not induce neutralizing anti-globulin responses. Chimeric antibodies have the further advantage of a prolonged *in vivo* half-life when compared with their murine counterparts and increased potency, as the human constant regions appear to be more effective at activating host effector functions.

Host effector mechanisms

When the MoAb reaches the target cell, the host effector mechanisms need to be intact and activated at the site of tumour infiltration. The use of unconjugated or 'naked' MoAbs relies on the ability of the antibody to mediate cell death either by delivering a direct apoptotic signal or by activating complement-mediated cell lysis or antibody-dependent cellular cytotoxicity (ADCC).[3] The ADCC response of the host varies and this may be related to polymorphisms of the IgG FC receptor gene.[4]

General strategies for MoAb therapy

Anti-idiotype antibodies

Early studies of Moab therapy were aimed at reducing cross-reactivity with normal cells by selecting target antigens that were entirely tumour-specific (Fig. 1). This approach is feasible in lymphoid malignancies through the production of anti-idiotype monoclonals directed against unique immunoglobulin or T-cell receptor molecules.[5] It is, however, limited by the necessity of producing reagents for each individual. Furthermore, idiotype-negative tumour cells readily emerge, thus preventing further therapy. An alternative anti-idiotype approach is to elicit a host anti-idiotype antibody response by the use of a vaccination strategy.

Unconjugated antibodies

The simplest, and, until recently, the most widely adopted use has been of unconjugated MoAbs, which target lineage-specific differentiation antigens. MoAbs have also been developed, which target cell surface

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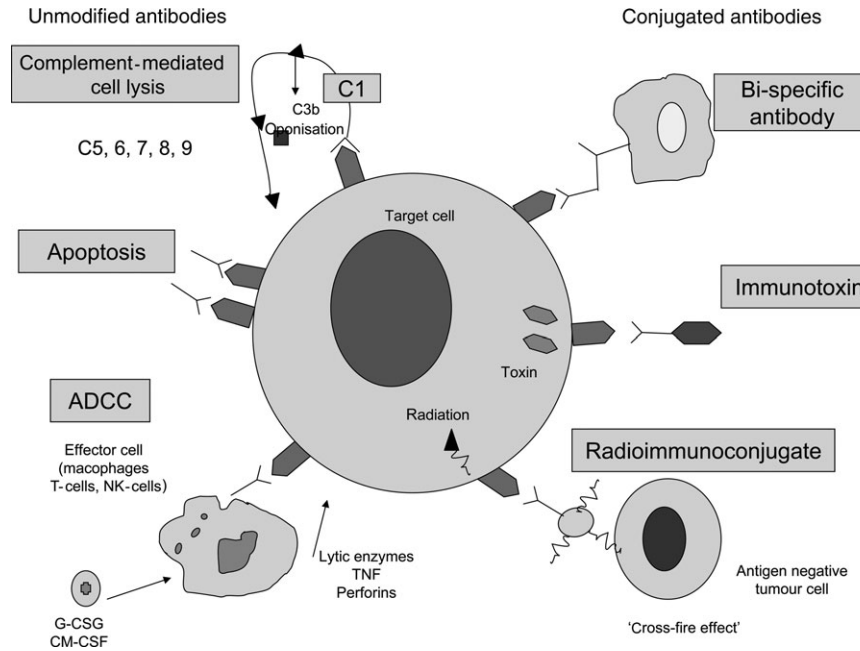

Fig. 1 Schema showing different mechanisms of action of unmodified and conjugated MoAbs.

receptors that regulate the growth of the tumour cells such as interleukin 2 or interleukin 6 receptors.

Conjugated antibodies

A third approach is to use MoAbs as 'vectors' to deliver agents that are directly cytotoxic, such as radio-isotopes, immunotoxins (ITs) or cytotoxic drugs or pro-drugs.

Radio-immunoconjugates (RICs) are the easiest of the conjugated antibodies to synthesize and have been used clinically both for disease detection and therapy of lymphoid neoplasms.[6] RICs have the advantage over unconjugated antibodies of potentially enhanced efficacy, particularly in bulky or poorly vascularized tumours. The MoAbs bind to the tumour-associated antigen and may trigger effector mechanisms in the same way as naked antibody. However, in this instance, the radio-isotope provides additional DNA damage by emitting α-, β- and γ-particles that have enough energy also to kill adjacent, antigen-negative, tumour cells. This 'crossfire' effect increases the overall toxicity to the tumour. The major obstacle to RIC therapy is the non-specific binding to normal host tissues. Only a fraction of the injected dose localizes in the tumour, with most being taken up by Fc

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and other receptors in the spleen, liver and lung. This contributes to toxicity as well as to depleting the therapeutic dose delivered to the target cell.

^{131}I and ^{90}Y are the two radionuclides most commonly used. Both emit β-particles and have relative advantages and disadvantages. (Table 1). ^{90}Y has higher energy and a longer path length, allowing deeper tissue penetration and tumour cell killing without direct antibody binding. It also has a shorter half-life making it more suitable for outpatient therapy. Unlike ^{131}I, however, ^{90}Y has no gamma emission and is not suitable for imaging. ^{111}In, which has comparable bio-distribution, is therefore used as a surrogate marker.

Immunotoxins

A variety of toxins have been conjugated to the variable regions of antibodies, including those derived from plants, such as ricin and saporin, and those derived from bacteria, such as diphtheria toxin and pseudomonas exotoxin.[7] Protein engineering has been used to modify the toxic moiety so that it is unable to bind to normal cells directly, but retains cytotoxic function. The antibody moiety directs the toxin to the target cell. In contrast to unconjugated MoAb–antigen complexes, which remain on the surface, ITs must be internalized so that the toxin can be liberated intracellularly. Molecule for molecule, toxins are much more potent than chemotherapy agents and can act at low concentrations to inactivate ribosomes and inhibit protein synthesis. This activity is seen against both resting and dividing cells. Most toxins are large molecules and, as a result, may not be well distributed within large tissue masses. For this reason, they may be most effective in a minimal residual disease setting. Furthermore, there are dose-limiting toxicities, including vascular leak syndrome, which often make this a less acceptable therapy. ITs are also strongly antigenic and rapidly induce high titres of human antibodies.

Table 1 Comparison of properties of the two radio-isotopes most commonly used in radio-immuno-conjugates.

Properties	^{131}I	^{90}Y
Path length	1–2 mm for β-component	5–10 mm
Energy	γ (0.36 MeV) and β (0.6 MeV) emitter	β-emitter (2–3 MeV)
Half-life	192 h	64 h
Metabolism	Some free ^{131}I released into blood	All retained in cell
Imaging	Can be used for both imaging and treatment	No γ-emission, additional RIC needed (^{111}In) for imaging/dosimetry
Administration	Inpatient (γ-emission is radiation hazard)	Outpatient

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Finally, bi-specific MoAbs[8] are engineered to include two different antibody-binding specificities. A single antibody is therefore able to target both the tumour cell and an immune-effector cell by including an antigen binding site for the tumour-associated antigen and a site for an effector cell epitope, such as CD3. This allows cross-linking of the T-lymphocyte with the tumour cells resulting in activation of cytotoxic mechanisms with the aim of enhancing cell kill. Bi-specific derivatives have been developed combining MoAbs (e.g. anti-CD20 and anti-CD30) with Fc receptors such as CD64, CD16 and CD89 and those that increase ability to recruit complement. Immunogenicity, both HAMA and non-specific T-cell activation, can occur with these antibodies.

Toxicity of MoAb therapy

Acute infusion-related reactions due to cytokine release (IL6 and TNF) are common, occurring in 50–90% of patients following the first administration of an antibody. These usually manifest as fever, rigors and nausea and tend to decrease with subsequent doses. Infusion reactions can be ameliorated by premedication with paracetomol and anti-histamines. Less commonly, urticaria, pruritis and bronchospasm may occur. Anaphylaxis is rare.

Many of the MoAbs directed against haemopoietic malignancies will deplete subsets of normal lymphoid and myeloid cells. Myelosuppression is usually transient, but lymphopenia may be very prolonged and be associated with an increased risk of infection and latent viral reactivation (e.g. cytomegalovirus and herpes virus).

Host humoural responses may be directed against the foreign antibody (HAMA) or against the toxin moiety in the ITs (e.g. human anti-ricin antibodies). This can occur even in profoundly immunosuppressed patients and leads to rapid clearance of the therapeutic antibody from the circulation, thus limiting the ability to re-treat individuals. This host response may also induce serum sickness.

The toxin moiety in ITs may also mediate endothelial injury, resulting in a vascular leak syndrome characterized by hypoalbuminaemia, peripheral and pulmonary oedema and hypotension. Most of the early studies of ITs reported this as a dose-limiting toxicity. Transient elevation of hepatic transaminases is also relatively common following IT therapy.

Clinical experience with MoAbs in lymphoid malignancies

The WHO classification separates the lymphoid malignancies on the basis of cell lineage, B- or T-cell types, into a large number of discrete

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Table 2 Major MoAbs used in the treatment of lymphoma.

Antibody	Antigen	Conjugate	Proven efficacy	Major references
Rituximab	CD20	None	FL, DLBCL and CLL in combination with chemotherapy, FL maintenance	10–24
Alemtuzumab	CD52	None	CLL, T-cell malignancies	25–29 34
Epratuzumab	CD22	None	In testing	30
Ibritumomab tiuxetan (Zevalin)	CD20	^{90}Y	Progression after rituximab	31
Tositumomab (Bexxar)	CD20	^{131}I	Progression after rituximab	32
Denileukin diftitox (Ontak)	IL-2R	Diphtheria toxin	MFs in relapse	36

disease entities with characteristic clinical, pathological, immunological and genetic features.[9] In each of these groups, both unconjugated and conjugated MoAbs are now available, which target specific lineage-associated antigens (Table 2).

B-cell malignancies

B-cell non-Hodgkin's lymphoma is one of the most common malignancies, with diffuse large B-cell lymphoma (DLBCL) accounting for about one-third of cases and follicular lymphoma (FL) for ~20%. The CD20 antigen is expressed on more than 95% of B-NHL, but not on other haemopoietic cells or stem cells. Rituximab, a chimeric anti-CD20 MoAb, has been widely used to treat this group of malignancy over the past decade.[10] Initial studies demonstrated that rituximab had activity in all types of relapsed and refractory B-NHL tested when used as a single agent. More recently, several large prospective randomized trials for patients with both FL and DLBCL have now demonstrated improved response rates and prolongation of remission when rituximab is incorporated into standard first-line chemotherapy. The impact of rituximab in conjunction with chemotherapy appears to be more than just additive. *In vitro* experiments in cell lines have shown that attachment of the antibody to cell surface CD20 initiates a signalling cascade followed by a decrease in bcl-2 and increase in some pro-apoptotic molecules. This may result in increased sensitivity of the cell to the effects of cytotoxic agents.[11]

Follicular lymphoma

For patients with FL, long-term disease-free remission, or cure, is rare. Most of these patients follow a remitting, relapsing course with a median OS of 8–10 years. More than 50% of patients die within

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5 years of first relapse. The majority of the early phase I and II studies of rituximab in B-NHL were conducted in patients with relapsed FL. These trials established a dose schedule of 375 mg/m^2 weekly for 4 consecutive weeks, which can safely be administered as outpatient therapy and resulted in overall response (OR) rates of up to 50% with a median time to disease progression (TTP) of around a year.[12]

The addition of rituximab was then examined in combination with chemotherapy (given on day 1 of each cycle), either combination regimens such as cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or cyclophosphamide, vincristine, prednisolone (CVP) or purine analogue-based therapies, for example, those which include fludarabine. All these studies suggested higher OR and complete remission (CR) rates, following the addition of rituximab to the standard chemotherapy regimens.[13] This observation has been confirmed in five large prospective randomized studies, including nearly 1000 patients, comparing chemotherapy with or without the addition of rituximab.[14–16] With improved OR and CR, these studies have consistently shown improved progression-free survival (e.g. TTP of 32 months for R-CVP versus 15 months for CVP, $P = 0.0001$[14] and not reached at 4 years for R-CHOP versus 2.6 years for CHOP, $P \leq 0.001$[16]) and improved overall survival for the chemo–immunotherapy combination (all now show increased OS, albeit modest). However, more than half of the patients with poor prognostic markers as defined by the follicular lymphoma international prognostic index (FLIPI) will relapse early. In the future, it may be possible to identify patients with poorer outlook using gene-expression profiling.

Rituximab maintenance treatment has been evaluated in several randomized controlled trials in both treatment-naive and -relapsed patients with FL after successful induction induction treatment with regimens consisting of chemotherapy alone, single-agent rituximab or rituximab plus chemotherapy.[17–20] The dose that has been adopted for induction therapy (375 mg/m^2) is generally given every 3 months until disease progression or for a maximum of 2 years. Short-term follow-up from two phase III studies suggest a survival advantage for rituximab maintenance therapy over observation, either in previously untreated or in relapsed patients.[19,20] In one European study of 465 relapsed FL patients, the median progression free survival (PFS) was extended from 14.9 to 51.5 months by the use of maintenance and 3-year OS was increased by nearly 10%.[19] However, one study comparing maintenance versus re-treatment with rituximab showed similar benefit for both strategies.[17] As yet, there is insufficient information regarding long-term toxicities, although one trial showed a slightly increased risk of infection. The optimal schedule, indication—first-line or relapsed patients—and duration of maintenance treatment are as yet undetermined.

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Diffuse large B-cell lymphoma

There is now evidence from three randomized trials[21,22] and a large retrospective analysis,[23] comparing CHOP alone with rituximab plus CHOP, showing a clear advantage for the chemo–immunotherapy combination. In older patients (over 60 years), the addition of rituximab resulted in a 19% improvement in EFS and 13% in OS.[22] In younger patients, a similar 20% improvement in EFS and OS at 3 years was reported.[23] For this reason, R-CHOP is now considered to be the standard first-line therapy in patients with DLBCL.[11] As in FL, those with patients with poor prognostic markers (high IPI) have a higher risk of relapse, often associated with a short PFS. In addition, those cases that are bcl-6-negative have an improved outcome with R-CHOP when compared with those that are bcl-6-positive. Patients with poorer prognosis may benefit from the addition of rituximab to more intensive regimens or from protocols incorporating novel agents.

Other B-NHL

Rituximab has also been used with good effect, both as a single agent and in combination, in mantle cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, MALT lymphoma, post-transplant lymphoproliferative disease, HIV-related B-NHL and primary cutaneous B cell lymphoma, but as yet, there are no randomized controlled trials reported in these rarer subtypes.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the commonest of the leukaemias and for many patients, the disease follows a benign course. However, for those patients who have progressive disease and are refractory to alkylating agent and fludarabine therapy, the median survival is of the order of 10 months. In CLL, two therapeutic MoAbs—rituximab and alemtuzumab—are now available for clinical use. Strategies that incorporate conventional chemotherapy with rituximab, which has only modest activity in CLL when used alone (ORR of 20–50%), appear to be particularly promising. Studies, using fludarabine and rituximab (FR)[24] and fludarabine, cyclophosphamide and rituximab (FCR)[25] have shown ORR of 90% and 95% and CR rates of 47% and 70%, respectively, in previously untreated patients, with 67% PFS at 4 years for FCR.

Alemtuzumab is a humanized anti-CD52, a target antigen that is widely expressed in both B- and T-lymphocytes. Although results on

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B-NHL have been disappointing, this antibody has greater efficacy as a single agent than rituximab in CLL, achieving ORR of 87% in previously untreated patients.[26] Most experience to date has been as a single agent in relapsed disease. An ORR of 30–50% is achieved in fludarabine-refractory patients, making this agent one of the most useful therapies in this disease setting, particularly for patients who do not have bulky nodal disease.[27] The efficacy of alemtuzumab in clearing blood and bone marrow (BM) makes it an attractive agent for purging residual BM infiltration after de-bulking therapy. More data are now emerging regarding the role of this antibody in such consolidation strategies,[28] showing improvement in responses (e.g. PR becoming CR) as well as prolongation in PFS in a randomized study for those receiving alemtuzumab consolidation, compared with observation. There are also a number of on-going trials evaluating alemtuzuamb in combination regimens.[29] In addition, alemtuzumab appears to be one of the only currently available therapies to have activity in CLL characterized by a p53 deletion[30] both as a single agent and in combination with high-dose steroids.[31] Case reports and small series have reported that these antibodies have induced responses in the rarer mature B-cell leukaemias, B-cell pro-lymphocytic leukaemia and Hairy cell leukaemia (HCL).

Other target antigens

Other antigens targeted in B-cell malignancies include CD19, 22, 23, 25 and 40. Humanized antibodies such as anti-HLA-DR (apolizumab) and anti-CD22 (epratuzumab) have been shown to be active in B-NHL. The latter modulates rather than depletes B-cells and appears to have some synergy with riuximab.[32] Several antibodies have also been developed as immuno-conjugates (e.g. CD19-ricin, CD22-pseudomonas exotoxin, DAB 389 IL-2 and CD40-pseudomonas exotoxin). Anti-CD22 IT has been shown to be effective in refractory HCL.[7]

Radio-immunotherapy of B-NHL

B-NHL is a particularly good candidate for radio-immunotherapy (RIT) because the disease is inherently radio-sensitive and the malignant cells in blood, BM, spleen and lymph nodes are readily accessible. Two radio-labelled anti-CD20 MoAbs, with comparable efficacy and toxicity, are approved for clinical use in treatment of B-NHL, ^{131}I-tositumomab (Bexxar®) and ^{90}Y-ibrutumobab tiuxetan (IDEC-Y2B8, Zevalin®).[33] Tumour targeting in RIT of B-NHL can be improved by pre-treatment with a cold antibody such as rituximab. This pre-dosing

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blocks non-specific binding of RICs by reticulo-endothelial cells and free antigen and improves tumour penetration.

In relapsed FL, response rates of 60–80% (CR 20–30%) are seen, with superior activity compared with rituximab in randomized trials. Higher RR (95–100%) and longer duration of response are seen when the RIT is used in previously untreated patients.[34] These conjugates have also been shown to improve RR and PFS when given as consolidation following chemotherapy for FL and this strategy is currently being tested in prospective randomized trials.

Myeloablative RIT supported by autologous stem cell rescue has been used successfully in relapsed FL[35] and was shown to be superior to conventional autograft in a cohort comparison.[36]

In DLBCL, there has been less experience with RIT than in FL with evidence for a 40–50% ORR in patients with relapsed or refractory disease and no randomized trials yet reported. On-going studies are examining the value of RIT as consolidation treatment after R-CHOP.

The toxicity profile of these RICs has been acceptable. The main toxicity is reversible myelosuppression with a late nadir occurring 6–10 weeks post-treatment. Pre-treatment BM involvement should not exceed 25%. HAMA responses, hypothyroidism and secondary malignancies have been reported.

T-cell leukaemias and lymphoma

The mature T-cell malignancies are a rare heterogeneous group of disorders, accounting for ~10% of all lymphoid neoplasms.[9] They can be broadly categorized into those with leukaemic, cutaneous, nodal or extra-nodal presentation (Table 3). Although some of the diseases in this group, such as T-cell large granular lymphocyte (T-LGL) leukaemia and early stage mycosis fungoides (MF), may follow a relatively benign protracted course, others have an aggressive clinical behaviour and a poor response to conventional chemotherapy. Apart from ALK + anaplastic large cell lymphoma, these are rarely curable malignancies and for many patients the survival is short (median of 6–8 months). There is a lack of consensus regarding treatment, and new therapeutic strategies are required to improve this poor prognosis.

Alemtuzumab

There are data indicating efficacy for alemtuzumab in T-cell prolymphocytic leukaemia (T-PLL), T-LGL, adult T-cell leukaemia/lymphoma (ATLL), peripheral T cell lymphomas (PTCL) and cutaneous T cell

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Table 3 Mature T- and NK-cell neoplasms: WHO classification.

1. Leukaemic/disseminated
(a) T-cell prolymphocytic leukemia (T-PLL)
(b) T-cell large granular lymphocytic leukemia (T-LGL)
(c) Aggressive NK-cell leukemia
(d) Adult T-cell leukemia/lymphoma (ATLL)
2. Nodal
(a) Peripheral T-cell lymphoma (PTCL), unspecified
(b) Angioimmunoblastic T-cell lymphoma
(c) Anaplastic large-cell lymphoma
3. Extranodal
(a) Extranodal NK-/T-cell lymphoma
(b) Intestinal (enteropathy-type) T-cell lymphoma
(c) Hepatosplenic ($\gamma-\delta$) T-cell lymphoma
(d) Subcutaneous panniculitis-like T-cell lymphoma
4. Cutaneous
(a) MFs/Sézary syndrome (SS)
(b) Primary cutaneous anaplastic large cell lymphoma
(c) Lymphomatoid papulsis

lymphoma (CTCL), used as a single agent and, more recently, in combination with chemotherapy.[37] Alemtuzumab appears to be particularly effective in T-PLL, an aggressive disease with a poor prognosis, achieving durable OR and CR of 76% and 60%, respectively, in relapsed patients. In the other T-cell leukaemias (T-LGL and ATLL), there are case reports indicating durable responses to alemtuzumab in patients with chemo-refractory disease. Alemtuzumab also has activity in patients with heavily pre-treated CTCL, with responses seen in 50–80% of patients, particularly those with erythroderma. More recently, trials have been undertaken of alemtuzumab in combination with conventional chemotherapy such as CHOP and fludarabine-based regimens, in the treatment of a range of PTCL.[38] Results have been promising, particularly in previously untreated patients, but follow-up is too short to establish whether this will have a favourable impact on PFS and survival. As yet, there are no randomized studies of chemotherapy versus chemo-immunotherapy.

Anti-CD25

The abnormal and activated T-cells in certain neoplasms express the IL2-R α-subunit identified by the anti-Tac (anti-CD25) MoAb. Normal resting cells do not express this antigen. ATLL is typically an aggressive incurable malignancy caused by the retro-virus, human T-cell lymphotropic virus 1 (HTLV1). Both unmodified anti-CD25 MoAb and radiolabelled antibody (^{131}I and ^{90}Y) have been used to treat patients,[39] showing activity in up to 50% of cases in phase I and II trials but with

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no randomized studies reported. The anti-CD25 antibody has also been fused to both diphtheria and pseudomonas toxins to form immuno-conjugates. Denileukin difitox (Ontak®) is a fused molecule targeting the high affinity IL2 receptor, which is widely used in the treatment of CTCL and is being tested in other lymphoid malignancies.[40] Pre-treatment with cytokines up-regulate the expression of the IL-2 receptor and may augment responses.

Other target antigens

Unmodified anti-CD5 and anti-CD4 have also been used to treat relapsed T-cell lymphoma. A humanized anti-CD4 has shown promising activity in the treatment of CTCL. A variety of immuno- and radio-immuno-conjugates have been constructed but have not yet found a clear therapeutic role.

Conclusion and future directions

Patients with haematological malignancies who have primary resistance or become refractory to standard chemotherapy have a poor prognosis. Studies of a number of MoAb treatments in this group of patients over the past decade have shown that 50% or more may be salvaged with such therapy. This represents an advance. Furthermore, there is now compelling evidence from large prospective randomized trials that the addition of MoAbs to standard chemotherapy regimens has the ability to enhance RR and improve survival for a significant number of patients with FL and DLBCL. Within the rarer B-cell and T-cell malignancies, the evidence is less well established with studies demonstrating efficacy in relapsed/refractory disease, but no prospective data from randomized controlled trials. Some of the challenges for the future include the following.

- *Determining the optimal clinical use of MoAbs* The optimal clinical setting, timing and dose schedules for the use of currently available antibodies are still uncertain. Prospective studies examining pharmacodynamics and kinetics may better inform future therapeutic use. Further trials are also required to examine the use of MoAbs as first-line therapy in some of the rarer NHL subtypes and as consolidation or maintenance treatment post induction therapy
- *Developing combination strategies* A further challenge will be to develop rational combination regimens which take advantage of the lack of cross-resistance and overlapping toxicities of different agents. Already, potential synergy has been exploited in the development of chemo–immunotherapy

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regimens such as R-CHOP in DLBCL. Naked and radio–immunoconjugated antibodies have been used in the consolidation setting following conventional chemotherapy to improve response rates and PFS. MoABs may also be combined with targeted small molecules such as proteosome inhibitors or biological agents such as interferons.

- *Advances in biotechnology* In the laboratory, there have been advances in antibody engineering, which enhance antigen binding and the ability to activate natural effector mechanisms. Subsequent generation antibodies are now becoming available in the clinic. Development of novel and improved targeted antibodies is expensive and this is reflected in the cost of antibody therapy. This may be prohibitive in some health economies.

There is no doubt that MoAb therapy now has an established place in the management of lymphoid malignancies. The clinical activity, relatively low toxicity and ease of administration make MoAbs an attractive option, used alone or in combination regimens. Over the next few years, more effective strategies for their use in clinical practice will be developed.

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