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Monoclonal antibody as therapy for malignant lymphomas

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Abstract

Rituximab was the first monoclonal antibody to have been registered for the treatment of B-cell lymphomas. Randomized studies have demonstrated its activity in follicular lymphoma, mantle-cell lymphoma, and diffuse large B-cell lymphoma in untreated or relapsing patients. Because of its high activity and low toxicity ratio, rituximab has transformed the outcome of patients with B-cell lymphoma. A combination of rituximab plus chemotherapy, R-CHOP, has the highest efficacy ever described with any chemotherapy in diffuse large B-cell lymphoma and follicular lymphoma. The role of radio-labelled antibodies is still to be defined. *To cite this article: B. Coiffier, C. R. Biologies 329 (2006).*

Résumé

Les anticorps monoclonaux dans le traitement des lymphomes malins. Le rituximab a été le premier anticorps monoclonal accepté par les agences du médicament pour le traitement des lymphomes à cellules B. Plusieurs études prospectives randomisées ont démontré son activité dans les lymphomes folliculaires, le lymphome à cellules du manteau et les lymphomes à grandes cellules B, et ceci dans le cas de patients en première ligne de traitement ou en rechute. Du fait de son activité importante et de sa faible toxicité, le rituximab a complètement modifié le traitement et le devenir des patients ayant un lymphome à cellules B. L'association du rituximab et d'une chimiothérapie standard, le R-CHOP, est le traitement présentant l'efficacité la plus importante jamais décrite pour le traitement des patients ayant un lymphome à grandes cellules B ou un lymphome folliculaire. Le rôle des anticorps combinés à une molécule radioactive ou des anticorps dirigés contre d'autres antigènes n'est pas encore bien défini. *Pour citer cet article : B. Coiffier, C. R. Biologies 329 (2006).*

1. Introduction

Non-Hodgkin's lymphoma is a heterogeneous group of B- and T-cell cancers, with a large variety of patterns of growth, clinical presentations, and responses to treatment. Its prognosis depends on histological subtype, tumour characteristics, host responses, and treatment.

About 90% of lymphomas have a B-cell phenotype and 10% a T-cell phenotype. Recent progress in the treatment of theses diseases came from the introduction

of monoclonal antibodies (mAb) alone or in combination with chemotherapy [1–3]. In lymphomas, the first antigen that has been targeted with success by mAb was the CD20 antigen, a trans-membrane protein expressed by more than 99% of B-cell lymphomas. Rituximab was the first approved mAb for the treatment of lymphoma patients. Through the last 10 years, clinical trials with rituximab have confirmed its efficacy in follicular lymphoma as well as in aggressive lymphomas and its use has expanded significantly beyond the initial indication of indolent B-cell lymphomas to virtually any CD20-positive lymphoma.

2. Mechanisms of action of mAb

The mechanisms of action of mAb differ with the antibody, the antigen it targets, and its use: alone, in combination with chemotherapy, or conjugated to a toxin or a radionuclide.

In case of a naked antibody, rituximab for example, different mechanisms have been identified [4,5]. CD20 binding by rituximab is followed by homotypic aggregation, rapid translocation of CD20 into specialized plasma membrane microdomains known as rafts, and induction of apoptosis. Membrane rafts concentrate *src* family kinases and other signalling molecules (phospholipases, caspases...), and the anti-CD20-induced apoptotic signals occur as a consequence of CD20 accumulation in rafts [6]. The role of complement-dependent cytotoxicity (CDC) is suggested by the consumption of complement observed after rituximab administration, but in vitro CDC does not correlate with clinical response [7,8]. CDC is probably involved in the cytokine-release syndrome and its toxicity [9]. The importance of antibody-dependent cellular cytotoxicity (ADCC) has been demonstrated in vivo when rituximab is used alone [10]. The Fc receptor (FcγR) of effector cells has two alleles and the valine/valine allele of FcγRIIIa, which confers a higher affinity for IgG1; rituximab is associated with an increased responsiveness to rituximab compared to the other alleles [10,11]. If the clinical relevance of the FcγRIIIa receptor dimorphism was established in a number of studies with rituximab used alone, it does not seem to play a major role when rituximab is used in combination with chemotherapy [12].

Modifications of the cellular signalling pathways by rituximab may be crucial for its clinical effect. The B-cell restricted cell surface phosphoprotein CD20 is involved in many cellular signalling events including proliferation, activation, differentiation, and apoptosis upon crosslinking. Monomeric rituximab chemosensitizes drug-resistant NHL cells via selective downregulation of antiapoptotic factors through the type II mitochondrial apoptotic pathway. In ARL (acquired immunodeficiency syndrome (AIDS)-related lymphoma), rituximab diminishes the activity of the p38MAPK signalling pathway resulting in inhibition of the interleukin (IL)-10/IL-10R autocrine/paracrine cytokine autoregulatory loop leading to the inhibition of constitutive STAT-3 activity and subsequent downregulation of Bcl-2 expression leading to chemosensitization [5]. Rituximab upregulates Raf-1 kinase inhibitor protein (RKIP) expression in non-ARL cells. Through physical association with Raf-1 and nuclear factor κB (NF-κB)-inducing kinase (NIK), RKIP negatively regulates two major survival pathways, namely, the extracellular signal-regulated kinase1/2 (ERK1/2) and the NFκB pathways, respectively [5]. Downmodulation of the ERK1/2 and NF-κB pathways inhibits the transcriptional activity of AP-1 and NF-κB transcription factors, respectively, both of which lead to the downregulation of Bcl-xL (Bcl-2 related gene (long alternatively spliced variant of Bcl-x gene)) transcription and expression and sensitization to drug-induced apoptosis. Bcl-xL-overexpressing cells corroborated the pivotal role of Bcl-xL in chemosensitization [5].

If some of these mechanisms may have a role when mAb are combined with a radionuclide, most of the antitumour effect resides in their capacity to deliver local radiotherapy after the mAb is attached to tumour cells [13]. The choice of antibody and therapeutic radioisotopes is critical for the success of radioimmunotherapy (RIT). Several radio-labelled mAb have been studied in clinical trials but only two, yttrium-90 (^{90}Y or Y-90) ibritumomab tiuxetan and iodine-131 (^{131}I or I-131) tositumomab, have been registered for the treatment of lymphoma patients. Both radio-labelled antibodies are mouse antibodies targeting CD20. Yttrium-90 is a pure β-emitter, with a half-life of 2.7 days [14]. It is linked to the antibody by a chelator (tiuxetan). The long path length of its β-particles is particularly advantageous in tumour with heterogeneous or low distribution of the antigen [15]. Iodine-131 is an α and β-emitter, it has a half-life of 8.0 days. The path length of its β-particles is relatively shorter than Y-90. Table 1 presents the differences between Y-90 and I-131 radio-labelled antibodies.

An alternative approach to increase the activity of mAb has been the development of immunotoxin, a construct conjugating the antibody to cytotoxic plant, bacterial toxic proteins, or chemotherapy drugs (doxorubicin) [16]. The commonly used toxins, ricin or diphtheria toxin are highly potent natural products that disrupt protein synthesis. Unlike unconjugated mAb, immunotox-

Table 1

Characteristics of the two registered radio-labelled mAb. Adapted from [14]

	^{90}Y-Ibritumomab	^{131}I-Tositumomab
Linker	tiuxetan	none
Isotope radiation decay	beta	beta and gamma
Half-life, days	2.7	8.0
Path length, mm	5.0	0.8
Energy (MeV)	2.3	0.61
Non tumour distribution	bone	thyroid
Urine excretion	limited	substantial
Imaging	not possible	possible

ins must be internalized after antigen binding to allow the toxin access to the cytosol. Although the conjugation to mAb confers some target specificity, the toxin continues to mediate non-specific toxicity to normal tissues. Deglycosylated ricin A-chain has been used to eliminate such non-specific toxicity.

3. Mechanisms of resistance

If multiple mechanisms of rituximab action have been reported, it remains unclear which is/are most important in patients, and therefore it is difficult to know the relative importance of potential mechanisms of resistance. This is true for the other mAb too. Conceptual approaches of resistance mechanisms may be resumed as followed [17].

Concerning events up to antigen binding, resistance to mAb effects may be secondary to low serum levels or rapid metabolism of the mAb; development of anti-monoclonal antibodies (HAMA), most frequent with non-humanized antibodies, or anti-chimeric (HACA) antibodies; possibly different distribution within malignant nodes, blood cells, marrow and extranodal sites and responsible for poor tumour penetration; high level of soluble antigen target (not yet demonstrated for CD20 antigen); high tumour burden; and poor surface antigen expression (case of chronic lymphocytic leukaemia [CLL] cells).

Events that may induce resistance to mAb after the antigen binding are alteration of induced intracellular signals, reduction of direct apoptosis effect in cases of elevated bcl2 protein (demonstrated for rituximab), inhibition of CDC by complement inhibitors (CLL), and alteration of cell-mediated immunity. Gene microarray analysis has shown that patients who failed to respond to rituximab have altered patterns of gene expression, with an overexpression of genes important in cell-mediated immunity [18].

4. Safety and tolerability

The safety of mAb is mainly related to its origin and to the compound attached to it. Radio-labelled mAbs have a greater haematological toxicity than naked mAbs because of the effect on surrounding normal haematopoietic cells in bone marrow. Immunotoxins have also a greater toxicity because of the release of the toxin. Some mAb such as alemtuzumab may have a larger haematological toxicity because the target antigen (CD52 in case of alemtuzumab) is not restricted to lymphoid cells.

All the mAbs have in common an infusion toxicity that was best described for rituximab. These side effects are observed during the infusion or in the first hours after drug infusion and particularly for the first infusion. They include fever, chills, dizziness, nausea, pruritus, throat swelling, cough, fatigue, hypotension, and transient bronchospasm in a majority of patients. These symptoms are part of the cytokine-release syndrome. Their intensity correlates with the number of circulating malignant cells at time of infusion. More severe infusional toxicity includes bronchospasm, angioedaema, and acute lung injury, often associated with high circulating cell counts or pre-existing cardiac or pulmonary disease. It seems that CDC of normal lymphocytes and lymphoma cells is the main mechanism of this toxicity and it is decreased in mAb with low CDC.

Another common toxicity is the rapid depletion of normal antigen-positive lymphocytes from blood, bone marrow and lymph nodes of the recipient, lasting between 3 and 6 months following the last administration of the mAb. In the case of rituximab, this depletion does not compromise immunity: immunoglobulins do not decrease significantly, and patients do not have an increased risk for infections during and after rituximab therapy [19], except for some viruses like herpes virus, cytomegalovirus, or hepatitis B virus. Maintenance treatment, particularly after autologous transplant, might be associated with a decrease in immunoglobulins [20].

5. Clinical studies

A few mAb have been registered for the treatment of lymphoma patients: rituximab (Rituxan® or MabThera®), ^{90}Y-ibritumomab tiuxetan (Zevalin®), ^{131}I-tositumomab (Bexxar®), and denileukin diftitox (OnTak®), the last two only in the USA. Alemtuzumab (MacCamapth®) is only registered for the treatment of CLL patients. However, a lot of other mAb are currently

in preclinical studies, phase-I or phase-II studies and summarizing the activity and the indication of all these new mAb is not easy. We will focus on demonstrated activity (phase-III studies) and some phase-II studies with promising results. Rituximab is certainly the mAb where the largest experience exists with several demonstrative randomized studies.

5.1. Rituximab in follicular lymphoma

5.1.1. Rituximab alone in relapsing patients

When used alone, rituximab is usually given as 4 weekly injections of 375 mg m^{-2} [21]. The pivotal multi-centre phase II study that included 166 patients treated with four infusions of rituximab showed an overall remission rate of 48% (including 6% of CR), and a median time to progression of 13 months [22]. Elevated β2-microglobulin, elevated LDH, bulky disease, and age higher than 60 years did not appear to impact the response, implying that patients regarded as having a poor prognosis may respond to rituximab. Median rituximab serum levels were significantly higher in responders, compared with the non-responders [23]. Mean serum antibody concentration was inversely correlated with the bulk of the disease and the number of circulating B-cells, suggesting that patients with a higher tumour load might need higher doses or prolonged treatment to achieve the necessary serum levels [24].

Patients relapsing after initial response to rituximab treatment may be retreated with comparable response rates and adverse side effects, but, interestingly, median time for progression might be longer than after first treatment [25,26]. Patients who progressed after rituximab re-treatment respond again to further courses [26].

The question of knowing whether rituximab maintenance is able to further improve response rates and to prolong remission duration is of considerable interest. The success of re-treatment or the strong correlation between rituximab plasma levels and response rates are in favour of such maintenance [23]. A recent randomized trial showed that adding maintenance doses of rituximab prolonged response duration: with a median follow up of 35 months, the median event-free survival (EFS) was prolonged in the treated group (23 months vs. 12 months in the control group) [27]. However, patients relapsed within the 6 months after stopping rituximab treatment. In another randomized study, Hainsworth showed that re-treatment at time of relapse or prolonged treatment have the same benefit in terms of duration of rituximab efficacy or time to chemotherapy [28]. A preliminary analysis of a German randomized study reported that rit-

uximab maintenance after R-FCM or FCM in relapsing patients significantly prolongs progression-free survival and overall survival [29].

Several questions remain without clear answer: what is the optimal prolonged treatment? What is the optimal duration maintenance? Which patients benefit from prolonged treatment? And, finally, is prolonged treatment or re-treatment at progression better in terms of survival or impact on transformation rate?

5.1.2. Rituximab alone in untreated follicular lymphoma

Usually, patients with no adverse prognostic factors are not treated until they develop such adverse parameters [30]. However, because of its low profile toxicity, its presumed low rate of secondary malignancy and its lack of stem cell toxicity, rituximab single-agent was investigated in this setting: in a series of 50 patients, a RR of 73% was obtained, with 26% of CR and 57% of the informative patients in CR reached a molecular remission [31]. However, even patients in CR and in molecular response did not seem to benefit from this treatment because the median time to progression was two years, not longer than without treatment. A randomized study is currently underway challenging this finding in these otherwise 'watch and wait' patients.

Rituximab alone was also studied in patients with a more aggressive presentation, needing treatment at diagnosis, or after some follow-up without treatment [32]. The RR, just after four infusions, was comparable with the one observed in relapsing patients (50% and less than 10% of CR). About 10% of patients had progressive disease during the immediate post-treatment period and progression occurred in less than 12 months among 50% of the responding patients. If this schedule has the favour of some physicians because it avoids chemotherapy, results are quite inferior to combination of chemotherapy and rituximab (see below) and no indication has yet been given regarding overall survival. In our opinion, it should not be recommended until randomized trials have compared it to the combined treatment.

5.1.3. Rituximab in combination with chemotherapy

Several randomized studies have now demonstrated that the addition of rituximab to standard chemotherapy regimens results in higher response rates and longer time to progression and event-free survival for patients treated with a combination of rituximab plus chemotherapy in first line or in first relapse patients (Table 2). In first-line patients, four studies have reported a benefit in terms of CR rates and PFS, although follow-up is

Table 2
Randomized studies comparing chemotherapy with the combination of rituximab and chemotherapy in patients with follicular lymphoma

Setting	Response rates	CR rates	Event-free survival	Time to progression	Overall survival
First-line patients					
Marcus [33]					
R-CVP	81%	41%	27 months	32 months	not
CVP	57%[**]	10%[**]	7 months[**]	15 months[**]	different
Hiddemann [87]					
R-CHOP	97%	20%	68 months	50 months	not analysed
CHOP	90%	17%	21 months[**]	15 months[**]	
Salles [36]					
R-CHVP-Ifn	not analysed	79%	not reached	not reached	not analysed
CHVP-Ifn		63%[**]			
Herold [35]					
R-MCP	85.5%	42%	not reached	not reported	not reported
MCP	65.5%[**]	20%[**]	19 months[**]		
Relapsing patients					
Forstpointner [37]					
R-FCM	79%	33%	not analysed	16 months	not reached
FCM	58%[**]	13%[**]		10 months[*]	24 months[**]
van Oers [38]				at 3 years	
R-CHOP	83%	30%	not analysed	68%	not significant
CHOP	72%[**]	18%[**]		31%[**]	
Adjuvant rituximab					
Hochster [39]					
CVP → R	not reported	30%	not reported	4.2 years	trend in favour
CVP		22%[*]		1.5 years[**]	of R

A second randomization studied maintenance therapy with rituximab and altered the results of first randomization for survival endpoints.

[*] $P < 0.05$.
[**] $P < 0.01$.

too short to detect an overall survival benefit [33–36]. The first study randomized patients between eight cycles of CVP and R-CVP. Overall and complete response rates were 81 and 41% in the R-CVP arm vs. 57 and 10% in the CVP arm, respectively ($P < 0.0001$). At a median follow-up of 30 months, patients treated with R-CVP had a highly significantly prolonged time to progression (median 32 months vs. 15 months for CVP; $P < 0.0001$). Median time to treatment failure was 27 months in patients receiving R-CVP and 7 months in the CVP arm ($P < 0.0001$) [33]. Overall survival is not yet different.

In the second study, patients were randomized between six cycles of CHOP and R-CHOP [34]. In 428 patients R-CHOP revealed a significantly higher RR (97 vs. 90%, $P = 0.011$) and a longer TTF (median not reached vs. 2.6 yr, $P < 0.0001$). In the second German study, patients with indolent lymphoma (56% follicular) were randomized between six cycles of MCP (mitoxantrone, cyclophosphamide, and prednisone) and R-MCP [35]. The overall response rate (RR) and the complete response rate (CR) for all patients was 85.5 and 42% in the R-MCP arm versus 65.5 and 20% in the MCP arm ($P < 0.0001$). EFS was significantly pro-

longed for patients receiving R-MCP vs. MCP alone ($P < 0.001$). Median EFS for MCP was 19 months and 73% for R-MCP. Follow-up was too short in these two studies for studying overall survival.

In the French study, patients were randomized between CHVP + interferon for 18 months and R-CHVP + interferon [36]. This first analysis of all patients demonstrated a significant improvement of response to therapy with R-CHVP + interferon compared to CHVP + interferon, both at 6 months [CR + CRru 49% vs. 76%; PR 36% vs. 18%; respectively ($P < 0.0001$)] and at 18 months [CR + CRu 79% vs. 63%; PR 5% vs. 10%; respectively ($P = 0.004$)]. In the control arm, estimated 2.5 yr EFS is 62% versus 78% with R-CHVP + interferon ($P = 0.003$).

In relapsing patients, a published study showed that R-FCM is superior to FCM alone [37] and another study was presented at 2004 ASH meeting with R-CHOP vs. CHOP alone (EORTC study) [38]. This last study is particularly interesting because preliminary results showed a benefit of R-CHOP over CHOP, but also a benefit of rituximab maintenance after CHOP only induction. The study continues to look at the effect of rituximab maintenance after R-CHOP.

Finally, one study reported that maintenance with rituximab in patients treated with chemotherapy increases CR rates and prolongs PFS [39]. However, the role of rituximab maintenance after a combination of rituximab plus chemotherapy remains unclear.

These different studies have implemented the use of combining rituximab with chemotherapy as standard treatment in patients with follicular lymphoma who need to be treated. Which one of the regimens is better is not yet demonstrated, but the comparison of CR rates, EFS and PFS from the different studies seems to show a larger benefit with the R-CHOP regimen. The comparison of results obtained with R-CHOP to those reached with rituximab only in the same type of patients equally favours the use of R-CHOP. However, these conclusions need to be taken with caution, because no randomized study has compared these different regimens and data for overall survival are not yet known.

5.1.4. Rituximab in combination with cytokines

Interferon$_{\alpha 2}$ has a direct anti-lymphoma activity and it also increases CD20 antigen expression on lymphoma cells and potentially augments the immune response induced by rituximab. Hence, its combination with rituximab could potentially represent an alternative to the rituximab-chemotherapy combinations. Currently only phase II studies or preliminary data are available, preventing any definitive conclusions [40,41]. Phase-I trials combining rituximab with other cytokines such as Interleukin-2, Interleukin-12, G-CSF and GM-CSF have shown promising preliminary results that need to be confirmed in phase-II trials [42,43].

5.2. RIT in follicular lymphoma

Two monoclonal antibodies combined with a radionuclide have been registered for the treatment of patients with relapsing/refractory follicular lymphoma. Radioimmunotherapy with Y-90- and I-131-labelled anti-CD20 antibodies (ibritumomab tiutexan and tositumomab) was associated with a high response rate in relapsing/refractory patients [44,45].

In the initial phase I/II study, ^{90}Y-ibritumomab was administered on 51 patients with relapsed and refractory CD20+ B-cell non-Hodgkin's lymphoma [44]. The dose of ^{90}Y-ibritumomab varied from 0.2 to 0.4 mCi kg^{-1}. The overall response rate (ORR) for the 34 patients with indolent lymphoma was 82% (complete response (CR) 26% and partial response (PR) 56%). The estimate median time to progression (TTP) for the entire group was 12.9+ months and the median duration of response was 11.7+ months. The major toxicity of ^{90}Y-ibritumomab

was myelosuppression, with thrombocytopenia being the most common. ^{90}Y-ibritumomab has been compared to rituximab in a randomized controlled phase III study [46]. In this study, 143 patients with relapsed or refractory indolent, follicular or transformed NHL were randomized to either standard dose rituximab or ^{90}Y-ibritumomab. The major endpoint of the study was to compare the overall response rate between the two drugs and the study was not powered to analyse response duration or other time-dependent variables. The ORR was 80% (CR/CRu 34% and PR 45%) for ^{90}Y-ibritumomab as compared to 56% (CR/CRu 20% and PR 36%) for rituximab ($P = 0.002$). The estimated TTP was 12.6 months for ^{90}Y-Ibritumomab and 10.2 months for rituximab ($P = 0.062$).

In another study, Witzig treated with ^{90}Y-ibritumomab 54 patients with follicular lymphoma refractory to rituximab [47]. Rituximab refractoriness was defined as no objective response or a TTP of less than 6 months for a precedent treatment with rituximab. The ORR for the entire cohort was 74% (CR 14% + PR 59%). The estimated TTP and response duration for responders were 8.7 and 6.4 months, respectively. Treatment was well tolerated and only one patient developed human antimurine antibodies (HAMA).

^{131}I-tositumomab has been studied for more than 10 years. Vose have reported the final results of a multicentre phase-II study with objectives to evaluate the efficacy, dosimetry, methodology and safety of ^{131}I-tositumomab [45]. Forty-seven patients with relapsed/refractory low-grade or transformed NHL were treated with ^{131}I-tositumomab. The ORR for the entire group was 57% with 15 (32%) patients achieving CR. The ORR was similar in patients with indolent (57%) or transformed lymphoma (60%). The median duration of response was 8.2 and 12.1 months respectively for each of these two groups. The treatment was well tolerated and haematologic toxicity was the principal adverse event. In the pivotal study, 60 patients with chemotherapy-refractory indolent or transformed CD20+ B-cell lymphoma (36 follicular, 23 transformed and 1 mantle cell) were treated with standard dose ^{131}I-tositumomab [48]. The ORR was 65% (CR 20% and PR 45%). The median duration of response was 6.5 months.

^{131}I-tositumomab has also been studied in a group of 76 patients with untreated follicular lymphoma [49]. Out of the 76 patients included, more than half did not have any criterion associated with poor outcome and correspond to patients that are usually not treated. CR was observed in 75% of the patients but only in 58% of those with a large lymph node. Median PFS was 6.1 years for all patients, but less for patients

Table 3
Randomized studies comparing CHOP with R-CHOP in patients with diffuse large B-cell lymphoma

	Coiffier [51,52]	Habermann [54]	Pfreundschuh [53]
Setting	60–80 years old	60–80 years old	< 60 years old
	No stage I	No stage I	IPI 0–1
	CHOP	Maintenance	CHOP or CHOP-like
Median follow-up	5 years	2.7 years	2 years
CR rates			
R-CHOP	75%	78%	85%
CHOP	63%[**]	77%	65%[**]
Early progression rates			
R-CHOP	9%	15%	16%
CHOP	22%[**]	17%	5%[**]
Relapses			
R-CHOP	34%	Not reported	Not reported
CHOP	20%[**]		
Event-free survival			Two-year TTF
R-CHOP	3.8 y	3.4 y	81%
CHOP	1.1 y[**]	2.4 y	58%[**]
Progression-free survival			
R-CHOP	Not reached	Not reported	Not reported
CHOP	1.0 y[**]		
Overall survival			Two-year OS
R-CHOP	Not reached	Not different	95%
CHOP	3.1 y[**]		85%[**]

A second randomization studied maintenance therapy with rituximab and altered the results of first randomization for survival endpoints.
[**] $P < 0.01$.

with criteria associated with poor outcome (details not given in the manuscript). This study only showed that patients without large tumour may respond well to ^{131}I-tositumomab, but it did not allow evaluating the role of this drug in patients with follicular lymphoma. Nothing being given for overall survival and given the toxicity associated with ^{131}I-tositumomab in relapsing/refractory patients, no recommendation is made for using it in untreated patients.

Even though ^{131}I-tositumomab has shown interesting results in phase-II study, duration of response is still limited. For this reason, some investigators are beginning to evaluate ^{131}I-tositumomab in combination with other form of therapy. In a phase-II study conducted by the SWOG [50], ^{131}I-tositumomab was combined with CHOP for the treatment of 90 patients with untreated follicular lymphoma. Patients received six cycles of standard CHOP followed by a consolidation dose of ^{131}I-tositumomab if PR was achieved. The ORR after ^{131}I-tositumomab was 90% (CR/CRu 67% and PR 23%). More interestingly, among assessable patients, 27 (57%) improved their level of response after ^{131}I-tositumomab. The estimated two-year progression-free survival (PFS) and overall survival were 81 and 97%, respectively (median follow-up 2.3 years). The two phases of the treatment were well tolerated. SWOG is currently

conducting a study comparing ^{131}I-tositumomab and rituximab in follicular patients treated with CHOP as first treatment. Only such a study may evaluate the benefit and toxicity of ^{131}I-tositumomab r in comparison with rituximab in first-line patients.

5.3. Other monoclonal antibodies

Several monoclonal antibodies directed against CD20 (hA20, HuMax-CD20, ocrelizumab) or other antigens (epratuzumab for CD22, apolizumab for HLA-DRB chain, galiximab for CD80) are currently in phases I or II. No definitive conclusion can be made on their activity, toxicity and benefit compared to rituximab. The real interest of these new antibodies will have to be demonstrated in randomized studies.

5.4. Rituximab in diffuse large B-cell lymphoma

The combination regimen R-CHOP, consisting of rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), is now considered as the standard treatment for treating young and elderly patients with diffuse large B-cell lymphoma because of the superior activity demonstrated in three randomized studies (Table 3). Results from the GELA study have

Table 4
Five-year survivals observed in the GELA study comparing eight cycles of R-CHOP and CHOP in elderly patients with diffuse large B-cell lymphoma [52]

	R-CHOP	CHOP	*P* value
Median event-free survival	3.8 years	1.1 years	= 0.00002
Five-year event-free survival	47%	29%	
Median progression-free survival	Not reached	1 y	< 0.00001
Five-year progression-free survival	54%	30%	
Median overall survival	Not reached	3.1 y	= 0.0073
Five-year overall survival	58%	45%	

been recently updated with a 5-year median follow-up and showed a persisting advantage for patients treated with R-CHOP (Table 4) [51,52]. Elderly patients treated with R-CHOP experienced a 62% increase in 5-year EFS, an 80% increase in PFS, and a 29% increase in overall survival compare to CHOP alone. This benefit was observed in all subgroups of patients, but was less important in patients with poor risk lymphoma, as defined by the International Prognostic Index.

The MInt study compared six cycles of R-CHOP-like chemotherapy to CHOP-like in young patients with a low-risk DLBCL [53]. After a median time of observation of 22 months, R-CHEMO patients had a significantly longer TTF ($P < 0.00001$), with estimated two-year TTF rates of 60% (CHEMO) vs. 76% (R-CHEMO). Complete remission (CR) rates of evaluable patients were significantly different (67% CHEMO vs. 81% R-CHEMO, $P < 0.0001$) as were the rates of progressive disease during treatment (15% vs. 4%, $P < 0.00001$). Similarly, overall survival was significantly different ($P < 0.001$), with two-year survival rates of 87% (CHEMO) and 94% (R-CHEMO), respectively.

The American study (ECOG/SWOG/CALGB study) was associated with a statistically benefit in the primary endpoint time to treatment failure (TTF) for the addition of rituximab to CHOP versus CHOP alone [54]. However, the complicated design makes conclusions difficult to compare with the two other studies: a double randomization looking at the effect of the same drug (rituximab). Furthermore, the administration of significantly less rituximab compared to the other studies may very well have contributed to the somewhat inferior results.

In a population-based analysis, the impressive efficacy results of the GELA trial can be repeated as the safety results be confirmed [55]: outcomes for patients with DLBCL were compared between two periods, CHOP then R-CHOP treatment recommendations. Both progression-free survival (risk ratio, 0.56; 95% CI 0.39–0.81; $P = 0.002$) and overall survival (risk ratio, 0.40;

95% CI 0.27–0.61, $P < 0.0001$) were significantly improved in the post-rituximab group. Two other studies have finished accrual and will be reported during the next meeting of the American Society of Hematology in December 2005. Both looked at rituximab combined with CHOP-14 and showed an advantage for rituximab-containing regimen (Pfreundschuh and Hagenbbek personal report).

If this R-CHOP regimen had a great activity in good risk patients, progresses still have to be made in the group of poor risk patients. Several ways are currently been tested, such as dose-dense and dose-intense regimens or the association of other biologics, such as bortezomib [1,56,57].

5.5. Other mAb in DLBCL

Very little is known about the efficacy of other mAb in DLBCL. A preliminary report of a study with ^{90}Y-ibritumomab in relapsing DLBCL patients [58]: it was a non-randomized, multicentre phase-II trial to evaluate the efficacy and safety of ^{90}Y-ibritumomab tiuxetan in elderly patients with histologically confirmed first relapsed or primary refractory DLBCL not appropriate for autologous stem cell transplantation. Patients were divided into two groups: those previously treated with chemotherapy alone [Group A, $n = 76$], and those previously treated with chemotherapy and rituximab [Group B, $n = 28$]. All patients received a single dose of ^{90}Y ibritumomab tiuxetan 14.8 MBq kg^{-1} (0.4 mCi kg^{-1}). The primary endpoint was overall response (ORR) assessed by using IWNHL criteria at weeks 6, 12, and 24. An ORR of 44% was observed in the entire study population. In Group A, the ORR was 52 and 19% in Group B. The median PFS was 6 months in Group A and 1.6 months for group B. Three patients died of suspected cerebral haemorrhage, preceded by grade-4 thrombocytopenia. If this study demonstrated an activity of the drug in DLBCL, this activity was low and short in duration, making it difficult to recommend it as a single agent for relapsing DLCBL patients when these patients will all have received rituximab before.

5.6. mAb in other lymphomas

5.6.1. Small lymphocytic lymphoma
The efficacy of rituximab alone in this lymphoma is not very well known, with few and discordant results. In a European trial in relapsing patients, the efficacy was low, with only a 10% RR [59]. In untreated patients, in contrast, Hainsworth found a 51% RR after 4

injections, with only 4% CR, and a median progression-free survival of 18.6 months [60]. Further studies are warranted to define the modality of use of rituximab monotherapy in this lymphoma, and its possible benefit. As SLL is closely related to chronic lymphocytic leukaemia (CLL), the use of rituximab in combination with fludarabine and/or cyclophosphamide should be tested because of its efficacy in CLL patients [61].

5.6.2. Marginal zone lymphoma

Mostly case reports have shown an efficacy of rituximab in these lymphomas, which seems comparable to what is observed in follicular lymphomas [62]. Efficacy was demonstrated in relapsing mucosa-associated lymphoid tissue (MALT) lymphoma [63]. A current IELSG (International Extranodal Lymphoma Study Group) trial randomizes chlorambucil vs. chlorambucil + rituximab in new or relapsing patients with MALT lymphoma.

5.6.3. Mantle-cell lymphoma

Mantle-cell lymphoma (MCL) has indolent lymphoma characteristics, but tends to pursue an aggressive clinical course and is incurable with standard chemotherapy. An interim analysis of a randomized trial comparing FCM (fludarabine/cyclophosphamide/mitoxantrone) to FCM plus rituximab has shown a striking improvement in RR with rituximab (65% vs. 33%; CR 35% vs. 0%), with a trend towards longer overall survival [37]. Interestingly, about one third of the patients achieved a molecular remission. Long-term remissions have been reported with intensive chemotherapy and autologous stem-cell transplantation plus rituximab (see below).

5.6.4. Chronic lymphocytic leukaemia (CLL)

Rituximab, given weekly as a single agent, has low activity in relapsing patients with CLL. A better activity has been observed in untreated patients [60]. Dose escalation, achieved by a thrice-weekly dosing schedule [64], or higher weekly doses, 500 to 2250 mg m^{-2} [65], is necessary to reach significant clinical activity, with a RR of respectively 45 and 36%, as a single agent. The concurrent administration of rituximab with fludarabine resulted in better results with a RR rate of 90%, with 47% CR [66]. The combination of rituximab with fludarabine and cyclophosphamide (FCR regimen) has demonstrated a great activity in untreated or relapsing patients in a single-centre phase-II trial: 70% of CR in untreated patients and 25% CR in previously treated patients [61,67]. A historical comparison among two studies from the CALGB showed that in multivariate analyses controlling for pre-treatment characteristics,

the patients receiving fludarabine and rituximab had a significantly better progression-free survival (PFS; $P < 0.0001$) and overall survival (OS; $P = 0.0006$) than patients receiving fludarabine therapy [68]. Two-year PFS probabilities were 0.67 versus 0.45, and two-year OS probabilities were 0.93 versus 0.81. A preliminary report showed that HuMax-CD20, a new humanized Mob targeting a different epitope of CD20 antigen, has promising activity [69].

Alemtuzumab is a humanized monoclonal antibody active against CD52. Compared to CD20, CD52 is expressed at much higher density on the surface of CLL cells. Activity of alemtuzumab in fludarabine-refractory CLL was established in the pivotal trial conducted by Keating [70]. Among 93 patients, the overall response rate was 33% including 2% complete responders. The median time to response was 6 weeks and the median time of therapy extended up to 8 weeks. Median survival of all patients was 16 months, but was 32 months for the responding patients. Use of subcutaneous alemtuzumab has been gaining ground over the intravenous formulation in recent years. In a study by Lundin, 41 patients with B-cell chronic lymphocytic leukaemia (B-CLL) received subcutaneous alemtuzumab injections as first-line therapy for up to 18 weeks [71]. The study demonstrated an overall response rate of 87% (19% CR; 68% PR). Complete remission or nodular PR in the marrow was achieved in 66%. Furthermore, subcutaneous alemtuzumab was better tolerated than the intravenous formulation. Clearance of some anatomic disease sites, particularly marrow, required extension of treatment duration of up to 18 weeks so that some patients benefited from a longer course of therapy. However, alemtuzumab does not seem to have a good activity in patients with large tumours.

5.6.5. Other lymphomas

Rituximab has been used successfully in lymphocyte predominant Hodgkin's disease [72] and in posttransplant lymphoproliferative disease [73]. No clear data exists for Burkitt's lymphoma.

The only yet reported randomized study without benefit in the rituximab arm was in patients with HIV-associated lymphoma: the TTF and OS were longer in R-CHOP arm, but not statistically different from those observed in CHOP arms [74]. More deaths after infection were observed in R-CHOP arm (14% versus 2%). However, this study did not have the power to show a significant difference between the two arms.

Alemtuzumab have been reported active in cutaneous T-cell lymphomas and peripheral T-cell lym-

phoma, but activity was low and of short duration in most of the cases [75,76].

The vast majority of the immunotoxin trials have been phase-I studies designated to determine the maximum tolerated dose. These trials have shown that therapeutic serum levels may be achieved with tolerable toxicity. A relatively uniform toxicity has been observed with vascular leak syndrome, hepatotoxicity, and myalgia. The different trials have shown a low response rate of 10 to 25% partial responses without durable efficacy. The only available immunotoxin (in the US) for treating patients is denileukin diftitox (OnTak®) for the treatment of cutaneous T-cell lymphoma: 30% of them responded with 10% of complete responses [77]. The future of this therapy will depend on decreasing toxicity, decreasing immune response against the construct, and on increasing the anti-tumour activity.

5.7. mAb and high dose therapy (HDT) with autologous stem-cell transplantation (ASCT)

Rituximab has been used as an in vivo purging agent before and as maintenance therapy after ASCT, in follicular and mantle-cell lymphoma [78,79] and in aggressive lymphoma [80], in first line or in relapse, with promising results. An ongoing international trial in relapsed and refractory aggressive lymphoma randomizes rituximab-DHAP (dexamethasone, aracytine, cisplatin) vs. rituximab-ICE (ifosfamide, carboplatin, etoposide) before ASCT and rituximab maintenance and observation for responding patients. Rituximab given after ASCT might have the interest to complete the remission and to further decrease the relapse rate. In a German study, CR rates developed overtime (57% at 6 months and 88% at 12 months), and after 2 years 29 out 30 patients were in persistent CR, whereas molecular response increased from 22% pre-transplant to 72% four weeks after rituximab and 100% six months after transplantation [81].

A few studies have looked at the potential use of radio-labelled monoclonal antibodies in the context of HDT. As compared to external TBI, a radio-labelled monoclonal antibody could theoretically permit to deliver a higher dose of radiation to the tumour, while limiting radiation dose to normal tissues, thus potentially reduce toxicity and treatment-related mortality [82]. Liu reported the results of 29 lymphoma patients (19 indolent and 10 aggressive) treated with ^{131}I-tositumomab as sole conditioning regimen before stem cell transplantation [83]. Patients received a median radiation dose to the tumour of 38 Gy (range 22 to 92 Gy). The estimated four-year overall survival and progression-free survival

were 68 and 42%, respectively. The treatment was well tolerated and the most common late complication was hypothyroidism developing in 17 of 29 patients. Press used myeloablative doses of ^{131}I-tositumomab in combination with chemotherapy [84]. In this phase I/II study, 25 Gy was considered the maximum dose of radiation that could be delivered to critical normal organs when combined with cyclophosphamide (100 mg kg^{-1}) and etoposide (60 mg kg^{-1}). They observed an objective response of 87% in a population of the patients with relapsed B-cell lymphoma (73% indolent lymphoma). The estimated two-year OS and PFS were 83 and 68%. These results were compared with those obtained for a similar population treated with cyclophosphamide–TBI–etoposide: in multivariable analysis OS and PFS were significantly longer for the group treated with radio-immunotherapy. The same protocol has also been studied in patients with relapsed mantle-cell lymphoma [85]. Gopal and co-workers observed a 73% complete response in a group of heavily pre-treated patients (median number of previous therapies: 3). Estimated three-year survival was 93% (median follow-up 19 months). The utilisation of ^{90}Y-ibritumomab tiutexan with the BEAM regimen (Z-BEAM) is also used in phase-II studies [86].

Although still preliminary, the results of RIT in the context of myeloablative therapy are interesting. Targeted RIT may be preferable to non-targeted external-beam TBI as regard to safety profile and clinical impact. Further studies will be needed to determine if radio-immunotherapy could definitively replace TBI in conditioning regimen for autologous and may be allogeneic stem cell transplantation.

6. Conclusion

Rituximab was the first monoclonal antibody registered in the treatment of lymphomas and it has allowed one of the major progresses for the treatment of lymphoma patients. Alone, it is a very well tolerated drug and it has a great activity in relapsing patients. However, it will hardly result in cure in this setting. In combination with chemotherapy, rituximab allowed for the highest response rates and longest event-free and overall survivals ever described in follicular and diffuse large B-cell lymphomas. It has activity but less well demonstrated in other B-cell lymphomas. Other monoclonal antibodies targeting CD20 or other antigens are on their way but their activity is not yet well defined. Radioimmunotherapy may add some specific activity but here too this is not well demonstrated. Antibodies conjugated with toxin or drug are less used for the moment.

Acknowledgements

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