Minireview

Clinical use of rituximab in haematological malignancies

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Rituximab is a chimeric human/mouse monoclonal antibody that is approved for the treatment of relapsed and refractory non-Hodgkin’s lymphoma (NHL) and in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy as first-line therapy for diffuse large B-cell NHL, where it has shown the first survival advantage over CHOP alone in more than 20 years. Strategies to help define the optimal therapeutic usage of rituximab are being assessed, including first-line and maintenance or extended therapy, and the combination of rituximab with chemotherapy in indolent NHL. Emerging data suggest that earlier use may yield higher response rates, extended therapy can prolong remission, and the addition of rituximab to chemotherapy can increase clinical and molecular remission rates when compared with those achieved using chemotherapy alone. Studies in the peritransplant setting suggest a role for rituximab in vivo purging prior to transplant and/or maintenance rituximab as a means of clearing minimal residual disease. Rituximab has also shown activity in other B-cell disorders such as chronic lymphocytic leukaemia.

The full potential of this immunotherapeutic agent remains to be defined in ongoing and future clinical trials.

Keywords: rituximab; haematological; malignancies

Combination chemotherapy has markedly improved outcome in aggressive non-Hodgkin’s lymphoma (NHL) since its introduction in the 1970s, but is curative in less than half of the patients. In indolent NHL, the impact of chemotherapy has been much lower; while response rates and progression-free survival (PFS) may be improved, overall survival (OS) has not increased and advanced indolent NHL remains essentially incurable without allogeneic bone marrow transplant.

A number of newer approaches to improve outcome are under investigation, including the use of monoclonal antibodies targeted against specific antigens expressed by lymphoma cells. The cell surface antigen CD20 is in many ways an ideal target: it is expressed by 95% of B-cell NHL cases but not on haematopoietic stem cells; it has a functional role in B-cell growth and also does not normally circulate as a free antigen in the plasma, so free antigen does not compete for antibody binding.

Rituximab is an anti-CD20 chimeric monoclonal antibody and was the first antibody approved for treatment of NHL. Multiple mechanisms of action for rituximab have been identified by in vitro studies. These include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and induction of apoptosis (reviewed by Maloney et al., 2002). Rituximab is also able to sensitise lymphoma cells to the cytotoxic activity of chemotherapy. There is now a substantial body of data describing the clinical use of rituximab in NHL, which we review here.

PREVIOUSLY UNTREATED INDOLENT NHL

Several studies have examined rituximab as a first-line therapy in patients with indolent NHL (Colombat et al., 2001; Witzig et al., 2002; Hainsworth, 2003). This treatment approach has yielded consistently high response rates (overall response rate (ORR) 61 – 73%, with 20 – 37% complete responses (CR)) (Colombat et al., 2001; Witzig et al., 2002; Hainsworth, 2003) (Table 1). It appears that extended therapy (induction followed by maintenance) may be better than rituximab induction only: recent 2-year follow-up data from a phase II trial of first-line and maintenance rituximab (Hainsworth, 2003) showed high ORRs and CRs (73 and 37%, respectively), and a median PFS of 34 months at a median 30-month follow-up. A phase III trial has compared maintenance therapy vs observation only following rituximab induction (Ghielmini et al., 2002). Of 202 patients enrolled, 151 responded or had stable disease following a 4-week course of rituximab, and were randomised to either rituximab maintenance (four once-weekly doses, every 2 months × 4) or to observation. At a median follow-up of 35 months, the rituximab maintenance group was found to have a 43% reduced risk of progression (median event-free survival (EFS) 23 vs 12 months; P = 0.02), with no increase in treatment-related adverse events. In the previously untreated patients, the difference in EFS was even greater (36 vs 19 months; P = 0.009).

The efficacy and tolerability of rituximab suggest that it may be particularly useful as a first-line single-agent therapy in elderly patients, and also in young women who want to preserve their fertility. It may also have a role as a first-line therapy in asymptomatic patients with advanced disease (stages 3 or 4), aiming to prolong the asymptomatic period. This will need to be assessed in clinical trials, however.

Rituximab plus chemotherapy in previously untreated indolent NHL

The single-agent activity of rituximab, coupled with its distinct mechanisms of action, nonoverlapping toxicity and ability to sensitise lymphoma cells to cytotoxic activity, has encouraged researchers to evaluate combinations of rituximab with che-
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| Disease setting        | Therapy                                      | n  | ORR (%) | CR (%) | Reference       |
|------------------------|----------------------------------------------|----|---------|--------|-----------------|
| Untreated indolent     | Single-agent rituximab                        | 50 | 73      | 27     | Colombat et al (2001) |
| Untreated indolent     | Single-agent rituximab                        | 60 | 47      | 7      | Hainsworth (2003) |
| Untreated indolent     | Single-agent rituximab                        | 37 | 62      | 44     | Witzig et al (2002)  |
| Relapsed aggressive    | Rituximab+PEPOCH                              | 50 | 64      | 26     | Jost et al (2001)  |
| Relapsed aggressive    | Rituximab+ICE                                 | 31 | 81      | 55     | Kewalramans et al (2001) |
| Relapsed aggressive    | Rituximab+paclitaxel/ topotecan               | 45 | 69      | 44     | Younes et al (2001) |
| Untreated CLL          | Rituximab+fludarabine                         | 104| 90      | 47     | Byrd et al (2003)  |
| Untreated CLL          | Rituximab+fludarabine                         | 30 | 90      | 33     | Schulz et al (2002) |
| Untreated/relapsed CLL | Rituximab+fludarabine/ cyclophosphamide       | 135| 95      | 67     | Wierda et al (2002) |

**RELAPSED INDOLENT NHL**

Rituximab is established in the treatment of relapsed indolent NHL, being both effective and well tolerated. The pivotal trial in this setting included 166 patients with relapsed low-grade or follicular lymphoma who were assigned to receive four once-weekly doses of rituximab 375 mg m⁻² (McLaughlin et al, 1998). The ORR was 48%, with a median time to progression (TTP) of 13 months in responders.

Prolonged single-agent rituximab (Piro et al, 1999) and/or retreatment (Davis et al, 2000) in patients with relapsed disease are both feasible and may have a beneficial effect on response rate and PFS. Extended rituximab therapy has been shown to achieve a response rate of 60% and a median disease-free survival in excess of 19 months (Piro et al, 1999), providing a rationale for maintenance rituximab in the first-line setting. These strategies may be particularly useful for patient groups such as the elderly, who may not be able to tolerate conventional chemotherapy or immunochemotherapy.

**Rituximab plus chemotherapy for relapsed indolent NHL**

Single-agent rituximab is active in patients with relapsed indolent lymphoma, but the remissions are no more durable than with conventional chemotherapy, and patients eventually relapse. Attempts to improve PFS by combining rituximab with chemotherapy are currently being undertaken. A study by the German Low-Grade Lymphoma Study Group is comparing the combination of fludarabine, cyclophosphamide and mitoxantrone (FCM) with rituximab plus FCM in patients with relapsed follicular and mantle cell lymphoma (MCL), and interim analyses have reported a response rate of 83% for the immunochemotherapy arm compared with 53% for FCM alone (Hiddemann et al, 2001), indicating that combined modality treatment may be superior to chemotherapy alone.

Many studies now suggest that combination immunochemotherapy may be more effective than single-agent rituximab or chemotherapy alone, and thus this treatment may be offered to patients with relapsed disease who can tolerate a combined regimen. However, the results of prospective comparative trials are still needed to confirm the superiority of immunochemotherapy in this setting.

**MANTLE CELL LYMPHOMA**

Patients with MCL have poor prognosis and curative treatment options are limited. As the majority of MCL express CD20, there is a clear rationale for the use of rituximab in this setting. A large, phase II study, assessing the efficacy of single-agent rituximab in 74 patients with newly diagnosed or relapsed MCL (34 and 40 patients, respectively), demonstrated a response rate of 34% with a median PFS of 14 months (Foran et al, 2000), confirming the activity of rituximab in MCL.

Given the poor prognosis of MCL, high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is being increasingly considered for patients achieving their first complete remission. Addition of rituximab to HDT/ASCT has been evaluated by Mangel et al (2002), who, in a matched pair analysis, showed that patients who received rituximab purging during intensive conditioning for ASCT achieved significantly better PFS, with a trend towards longer OS, than historical controls who received...
conventional chemotherapy (anthracycline or cyclophosphamide/fludarabine). Another study in this setting found that all 20 assessable patients achieved lymphoma-free stem cell harvests (by PCR analysis) following intensified induction with rituximab in vivo purging, while 26 of the 28 patients were alive and disease-free at a median follow-up of 22 months (Gianni et al., 2002). Romaguera et al. (2001) treated 77 patients with previously untreated MCL, with a combination of rituximab plus HyperCVAD. A response rate of 89% was obtained and, interestingly, failure-free survival and OS in younger patients were similar to that previously achieved using the HyperCVAD regimen in combination with HDT/ASCT. The addition of rituximab to the HyperCVAD regimen may, therefore, result in durable remissions without the need for ASCT.

RITUXIMAB IN AGGRESSIVE NHL

The activity of single-agent rituximab in relapsed aggressive NHL has been demonstrated, but the strongest data in aggressive NHL have come from studies of combination immunochemotherapy, particularly rituximab plus CHOP (R-CHOP). Vose et al. (2001) reported a response rate of 94%, with 61% CR, for R-CHOP in 33 patients with previously untreated aggressive NHL. Long-term (median 62-month) follow-up of these 33 patients has recently reported an OS and PFS of 87 and 80%, respectively (Vose et al., 2002).

A prospective randomised trial in 399 elderly patients (aged 60–80 years) with previously untreated diffuse large B-cell lymphoma (DLCL) demonstrated a significant advantage for R-CHOP over CHOP alone (Coiffier et al., 2002). Patients in the R-CHOP group had a higher CR rate (75 vs 63%, P = 0.005), improved PFS (2-year disease progression 9 vs 22%, P = 0.007; 2-year relapse rate 14 vs 25%, P = 0.002) and increased EFS and OS (2-year EFS 57 vs 38%, P = 0.001; 2-year OS 70 vs 57%, P = 0.007). No significant difference in treatment-related toxicity was seen between the groups. In an interim subset analysis of 328 patients, it was shown that R-CHOP was superior to CHOP alone in both low-risk and high-risk patients, and also in patients aged 60–70 or 70–80 years (Coiffier et al., 2001). This study has identified R-CHOP as the gold standard therapy in elderly patients with DLCL and the results of a similar ongoing study in younger patients are awaited (MINI).

Rituximab for relapsed aggressive NHL

HDT followed by ASCT is the preferred treatment for younger patients with relapsed aggressive lymphoma that is responsive to conventional salvage regimens. Several studies have shown good ORRs and CRs (ORR 60–80% with CR 25–60%) in patients treated with a rituximab-containing salvage regimen which appear superior to those achieved with chemotherapy alone (Table 1).

RITUXIMAB IN STEM CELL TRANSPLANTATION

While HDT/ASCT may be considered a potentially curative therapy for aggressive NHL, approximately 40–60% of patients with aggressive NHL, and most patients with indolent NHL, will eventually relapse following transplant. Relapse post-transplant is due either to contamination of the stem cell harvest or persistence of MRD post-HDT. A number of strategies have therefore been employed in attempts to prevent/reduce stem cell contamination (stem cell purging) and/or eradicate lymphoma cells that survived HDT (post-transplant ‘mopping up’).

Patients with follicular lymphoma whose bone marrow harvests are cleared of bcl-2-positive cells have increased relapse-free survival compared with patients whose bone marrow harvests remain positive (Freedman et al., 1999). Whereas the efficacy of immunological ex vivo purging (using monoclonal antibodies) is limited (up to 58% of harvests remain bcl-2 positive), in vivo purging with rituximab has produced bcl-2-negative harvests in 69–90% of stem cell harvests without compromising stem cell yield or function (reviewed by Gisselbrecht and Mounier, 2003).

Rituximab in vivo purging pretreatment results in a high rate of molecular remissions post-transplant, and favourable PFS (reviewed by Gisselbrecht and Mounier, 2003). A number of studies have demonstrated an increase in molecular remission using rituximab post-transplant (Horwitz et al., 2001; Brugger et al., 2002), but it remains to be seen whether these translate into durable clinical remissions. Whether there is, in fact, a significant survival advantage using rituximab peritransplant, however, remains to be determined in prospective randomised studies. The ongoing EBMT Lymp-1 trial randomised patients with follicular lymphoma to receive ASCT with or without in vivo purging with rituximab, as well as to post-transplant rituximab vs observation. This and other ongoing studies in both indolent and aggressive NHL will help to define the role of rituximab in the peritransplant setting.

RITUXIMAB IN CHRONIC LYMPHOCYTIC LEUKAEMIA

The efficacy and tolerability of rituximab have been evaluated in other haematological disorders, most notably chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL), the lymphomatous equivalent of CLL. However, single-agent rituximab has yielded low response rates (approximately 15%) in patients with relapsed CLL/SLL (McLaughlin et al., 1998; Piro et al., 1999). In contrast, the response rate in patients with previously untreated CLL/SLL was much higher (56%, with 8% CR) (Hainsworth, 2003). Given the low responses seen in relapsed disease, increased dosing and dose escalation have been evaluated as strategies to increase response to rituximab (Byrd et al., 2001; O’Brien et al., 2001). Both were shown to increase response rates to between 45 and 75%, but these strategies are not feasible in routine medical practice. The combination of chemotherapy with rituximab appears to be well tolerated and effective in CLL. Studies of rituximab with fludarabine-containing regimens, based on previous data showing an in vitro synergy between fludarabine and rituximab (Alas et al., 2000), reported high response rates of 90–95% (CR of 33–67%) (Schulz et al., 2002; Wierda et al., 2002; Byrd et al., 2003) (Table 1). The impact of these clinical responses on PFS and OS remains to be determined.

RITUXIMAB IN OTHER HAEMATOLOGICAL DISORDERS

Rituximab has been evaluated in a range of other B-cell malignancies, including post-transplant lymphoproliferative disorder (PTLD), Waldenström’s disease and HIV-associated lymphoma. Data from two studies indicate that approximately 50% of the patients with PTLD may respond to rituximab monotherapy, and CRs of 33 and 52% have been reported (Choquet et al., 2002; Oertel et al., 2002). Rituximab has produced response rates of 40–86% in Waldenström’s macroglobulinaemia with some evidence for CRs, especially when used in combination with fludarabine (Byrd et al., 1999; Treon et al., 2002). Patients with HIV-related NHL have shown very encouraging responses to rituximab with ORRs and CR rates of approximately 80% (Boue et al., 2002). Although patient numbers are low, the data for rituximab in lymphocyte predominant Hodgkin’s disease are also encouraging. Rituximab has also been evaluated in nonmalignant B-cell disorders. In immune thrombocytopenic purpura (ITP), single-agent rituximab has demonstrated responses in up to 72% of patients, with CR in 32% and a response duration of 12+ months for patients in CR (Cooper et al., 2002). The highest response rates
have been seen in patients with refractory ITP (Cooper et al, 2002), suggesting that rituximab may be a valuable agent for patients with few other treatment options. Promising results have also been demonstrated in autoimmune haemolytic anaemia, where all patients have responded to both treatment and retreatment with rituximab (Gupta et al, 2001). Taken together, the studies indicate the potential of rituximab in B-cell disorders, and the need for further assessment of its efficacy and tolerability in these settings.

**TOLERABILITY OF RITUXIMAB**

Single-agent studies have reported the good tolerability of rituximab. The most common adverse events are infusion-related reactions, comprising mainly fever and chills, in more than 50% of patients. These occur usually within hours of the first infusion and are rare with subsequent infusions. No significant increase in infusion-related reactions is seen in patients treated with rituximab plus chemotherapy. In the phase II trial of rituximab plus CHOP vs CHOP alone, grade 3 or 4 infusion-related reactions were seen in 9% of patients in the rituximab plus CHOP arm, but all were able to complete planned therapy with no further recurrence of severe infusion-related reactions (Coiffier et al, 2002). Subgroups of patients who may be at higher risk of rituximab-associated adverse events have been identified. Patients with high tumour burden are at increased risk of tumour lysis syndrome. Those with existing or prior pulmonary or cardiac complications should also be treated with caution and monitored because of infusion-related reactions.

Single-agent rituximab induces B-cell depletion in the majority of patients (McLaughlin et al, 1998). Given this B-cell depletion, monitoring of infections has been undertaken. During treatment in the McLaughlin trial (single-agent rituximab in relapsed low-grade and follicular NHL), 50 of 166 patients developed 68 infectious events (McLaughlin et al, 1998). Of these, six events (only 9%) were grade 3 and none grade 4. Prolonged B-cell depletion with maintenance rituximab also does not seem to result in a significant increase in infections (Ghielmini et al, 2002; Hainsworth, 2003). Furthermore, combination studies indicate that the addition of rituximab to chemotherapy does not significantly increase clinically relevant toxicity. In the phase III study of rituximab plus CHOP vs CHOP (Coiffier et al, 2002), the incidence of grade 3 or 4 adverse events was very similar in both arms.

Data on the development of human anti-mouse (HAMA) or human anti-chimeric antibody (HACA) are available (Rituximab Summary of Product Characteristics). Of 67 patients evaluated for HAMA, no responses were observed; of 356 evaluated for HACA, 1.1% (four patients) were positive. These data indicate that retreatment or maintenance therapy with rituximab remains feasible: patients may continue responding to repeated rituximab exposure without developing immune resistance.

**FUTURE DIRECTIONS**

Several trials are ongoing or planned in order to better define the role of rituximab in therapy for indolent (Table 2) and aggressive NHL (Table 3) and for other B-cell disorders. In the indolent setting there is a growing focus on first-line evaluation, combination therapy with either chemotherapy or other biological agents, and rituximab maintenance therapy. Of note is the EBMT Lym-1 trial assessing rituximab in the peritransplant setting both as an in vivo purge and as maintenance therapy. A BNLI trial of rituximab vs watchful waiting in patients with advanced-stage asymptomatic indolent NHL is planned.

In aggressive NHL, data from two ongoing trials are awaited with interest to confirm the clinical benefit of adding rituximab to CHOP (or CHOP-like therapy) for elderly patients (ECOG 4494) or younger patients (MInt) with untreated DLCL (Table 3). Several smaller phase II studies are evaluating the efficacy of rituximab in other B-cell disorders, one of which, central nervous system lymphomas, presents a particular challenge.

In summary, rituximab has shown efficacy and tolerability as monotherapy in indolent NHL. The data suggest that patients treated earlier in the course of their disease may respond better to therapy and that maintenance therapy may provide additional benefit. In both indolent and aggressive NHL, the use of rituximab with chemotherapy may provide an advantage over chemotherapy alone and this is reflected in the number of current and planned studies of immunochemotherapy. The survival benefit for rituximab plus CHOP over CHOP alone demonstrated in the GELA study is awaiting full confirmation by the MInt and ECOG trials in elderly and younger patients with untreated DLCL. The general trend seen in NHL is for improved response rates and quality of response when rituximab is added to chemotherapy; whether this will translate into improved survival will be

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**Table 2** Ongoing studies of rituximab in indolent NHL

| Group/study                | n   | Treatment                                                                 |
|----------------------------|-----|---------------------------------------------------------------------------|
| Nordic lymphoma group      | 318 | Rituximab induction + interferon in untreated indolent NHL. Patients with partial or minor response receive further rituximab induction + interferon |
| ECOG 1496                  | 515 | Rituximab maintenance after CVP in untreated indolent lymphoma            |
| EORTC-2098I                | 600 | CHOP + rituximab + maintenance treatment in relapsed follicular NHL       |
| EBMT Lym-1                 | 460 | Rituximab purging and maintenance therapy with ASCT in relapsed follicular NHL |
| M9021                      | 322 | CVP + rituximab in untreated indolent lymphoma                            |

**Table 3** Ongoing studies of rituximab immunochemotherapy in aggressive NHL

| Group/ study | n   | Treatment                                                                 |
|--------------|-----|---------------------------------------------------------------------------|
| ECOG 4494    | 631 | CHOP & rituximab & maintenance in older patients with diffuse large cell NHL |
| MInt         | 820 | CHOP & rituximab in younger untreated patients with DLCL                   |
| AMC-010      | 880 | CHOP & rituximab in untreated HIV-associated NHL                            |
| RICOVER 60   | 400 | 2 × 2 factorial design. CHOP 14 & rituximab and six vs eight cycles of chemotherapy (eight doses rituximab) in older patients with untreated aggressive NHL |
| CORAL trial  |     | Rituximab + ICE vs rituximab + DHAP in relapsed aggressive NHL followed by HDT/ ASCT. Second randomisation to rituximab maintenance vs observation |
determined by longer-term follow-up of completed studies. Transplantation studies indicate that rituximab in vivo purging is active and does not compromise ASCT although the role of both in vivo purging and post-transplant maintenance remains to be defined. One characteristic central to the integration of rituximab in these diverse clinical settings is its ability to achieve not only clinical but molecular responses—the mechanisms of action of this monoclonal antibody underpin its potential and utility in the treatment of CD20-positive disorders. An improved understanding of these mechanisms and the molecular basis of NHL will help the full therapeutic potential of this agent to be realised.

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