Mantle cell lymphoma (MCL) is a rare, aggressive, distinct subtype of B-cell non-Hodgkin's lymphoma (NHL), usually occurring in older adults. In most patients the tumour has an aggressive behaviour, and the majority present with advanced-stage disease.

MCL usually responds to chemotherapy, only to relapse frequently, with a much shorter duration of response, time to progression, and overall survival compared to follicular NHL. The treatment approach for newly diagnosed patients generally depends on whether they are transplant-eligible. Only a small minority of patients achieve sustained remission after first-line therapy, and sequential therapies must normally be used.

For years the standard treatment for patients with MCL has been polychemotherapy, mainly with CHOP but also with hyper-CVAD, fludarabine-containing regimens and other combinations. Rituximab, an antibody directed against the CD20 antigen which is universally expressed by MCL cells, has been studied both in combination with existing chemotherapeutic regimens and as monotherapy in the treatment of MCL. This review presents a summary of the main data published to date for rituximab in the treatment of MCL.

Summary

Background

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Literature

A search of Medline and Embase was conducted (latest search date: 9/5/2011); other sources consulted included NHS Evidence, Micromedex, AHFS Drug Information, and the National electronic Library for Medicines.

Efficacy studies

Several studies have confirmed that single-agent rituximab has only moderate activity in the treatment of MCL. There are also a number of studies evaluating the addition of rituximab to chemotherapy for the treatment of MCL, including three Phase III studies.

One Phase III study evaluated the addition of rituximab to CHOP chemotherapy (R-CHOP) in the first-line treatment of adults with advanced follicular lymphoma, MCL, or lymphoplasmacytic lymphoma. The published results were based on the MCL subgroup (n=122) – the overall response rate was 75% with CHOP and 94% with R-CHOP (p=0.0054), with a complete response seen in 7% and 34%, respectively (p=0.00024). Despite this, no benefits on progression-free survival or overall survival were demonstrated.
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A second, open-label Phase III study (n=147) evaluated the addition of rituximab to FCM chemotherapy in adults with relapsed or refractory follicular (n=72), mantle cell (n=52) or lymphoplasmocytoid (n=16) lymphoma. The overall response rate was higher in the R-FCM group (33% CR and 45% PR) than the FCM group (13% CR and 45% PR) overall (p=0.01). Overall survival (not reached at 3 years for the R-FCM group versus 24 months for FCM; p=0.003) and progression-free survival (16 months versus 10 months, respectively; p=0.0381) were also improved. The difference in overall response between the two groups was not statistically significant for the MCL subgroup; neither was the difference in median progression-free survival (8 months for R-FCM and 4 months for FCM; p=0.3887). The difference in median overall survival was however statistically significant (not reached for R-FCM versus 11 months for FCM; p=0.0042).

Those who responded (CR or PR) were re-randomised to treatment with two further 4-week courses of rituximab (at three and six months) or to observation only. After a median follow-up of 26 months, the median progression-free survival after end of induction had not been reached in the R-maintenance arm compared to 17 months in patients who received no further treatment (p<0.001). When restricting the analysis to those who had initially received R-FCM and to those with MCL, the median PFS values were 14 months versus 12 months, respectively (p=0.049).

The third Phase III study (n=358) evaluated the addition of rituximab to MCP chemotherapy in the first-line treatment of advanced stage follicular lymphoma, lymphoplasmacytic lymphoma or MCL. The results, reported in abstract form only, show that the rate of overall response and CR for all pts was 85.5% and 42% in the R-MCP arm versus 65.5% and 20% in the MCP arm (p<0.0001). Median event-free survival was 19 months for both groups and estimated two-year event-free survival was 69% for R-MCP versus 44% for MCP (p<0.0001). No results for the MCL subgroup were reported.

A number of uncontrolled studies are also available and are summarised in the report (see Table 2).

Health economics

No published cost-effectiveness analyses were identified.

Critical evaluation/ Issues for consideration

There have been a number of trials of varying quality assessing the addition of rituximab to chemotherapy regimens in the treatment of MCL. Three of these are Phase III trials (one available in abstract form only) - assessing rituximab added to CHOP (first-line), MCP (first-line), and FCM (relapsed/refractory).

The only Phase III trial to exclusively enrol patients with MCL was that comparing CHOP to R-CHOP as induction treatment; this found that addition of rituximab improved the ORR and lengthened time to treatment failure, but there was no observed improvement in progression-free or overall survival.

The Phase III trial evaluating rituximab added to FCM versus FCM alone in advanced, pre-treated disease looked at different lymphomas; 35% were MCL. R-FCM was associated with a higher ORR compared to FCM alone, but this was not statistically significant. The use of rituximab maintenance in the MCL patients resulted in a 2-month improvement in PFS but this was of borderline significance. The study was not powered to detect differences in outcomes for each separate subgroup of lymphoma.

The study evaluating the addition of rituximab to MCP also included a number of lymphoma types; the study has been reported in abstract form only and did not present results for the MCL subgroup.

In general, the ORR when rituximab is added to chemotherapy in MCL is lower than that observed for other B-cell lymphomas (e.g. follicular lymphoma); this reflects the generally lower response to treatment overall in this subgroup.

The recently published Phase II trial from the Nordic Lymphoma Group appears to be the most promising in terms of use of rituximab around auto-SCT – when compared to a historical group who received no rituximab (and also no high-dose cytarabine), the EFS, OS and PFS were increased. Further studies directly comparing such regimens with or without rituximab (rather than comparison with historical controls) are desirable.

Single agent rituximab has only moderate activity in MCL but may be an option for the treatment of patients who have contra-indications to systemic chemotherapy or who have significant co-morbidity.
Introduction

Background

Mantle cell lymphoma (MCL) is a rare, aggressive, distinct clinicopathological subtype of B-cell non-Hodgkin’s lymphoma (NHL). It usually occurs in older adults (median age of presentation is 60 years), and has a male predominance (1). The median overall survival of patients with MCL who do not have a stem cell transplant (SCT) is 3-5 years, which is significantly shorter than that seen with other lymphomas (2). Its genetic hallmark is the t[11;14](q13;q32) chromosomal translocation, which leads to over-expression of the cyclin-D1 protein in tumour cells. The immunophenotype resembles that of a mature B cell, including CD20+ (2, 3).

In 2004 there were 10,003 people diagnosed with NHL in the UK; this corresponds to an age-standardised incidence rate of 13.4 per 100,000 population (15.7 for males and 11.4 for females) (4). MCL accounts for approximately 6% of all cases of NHL, which would correspond to an approximate incidence rate of <1 case (0.8) per 100,000 in the UK.

The Ann Arbor staging system used to be the major determinant of therapy in NHL, and was based entirely on the anatomical extent of disease (4). The International Prognostic Index (IPI) was developed more recently to provide a predictive model for aggressive NHL based on presenting features, and an index specific to mantle cell lymphoma is also now available (Mantle Cell International Prognostic Index – MIPI) (5). The MIPI scores range between 0-11 possible points; those with 0-3 points are classified as low risk, 4-5 points are intermediate risk, and ≥ 6 points are high risk.

<table>
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<th>LDHULN</th>
<th>WBC (10⁹/l)</th>
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ECOG PS = Eastern Cooperative Oncology Group performance status; LDHULN = lactic acid dehydrogenase institutional upper limit of normal; WBC = white blood cell count

Management

Although some patients with MCL may follow an indolent clinical evolution, in most the tumour has an aggressive behaviour. The majority of patients present with advanced-stage disease, which warrants systemic treatment (3). Like follicular NHL, MCL usually responds to chemotherapy, only to relapse frequently. Unlike follicular NHL, however, the duration of response (DR), time to progression (TTP), and overall survival (OS) for MCL are much shorter (5). As recent studies have shown that the early use of SCT can lead to long-term survival in MCL, and the treatment approach for newly diagnosed patients generally depends on whether they are transplant-eligible (5). Only a small minority of patients with MCL achieve sustained remission after first-line therapy, and sequential therapies must normally be used (6).

For years the standard treatment for patients with MCL has been polychemotherapy, mainly with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) but also with hyper-CVAD, fludarabine-containing regimens and other combinations (7). Rituximab, an antibody directed against the CD20 antigen which is universally expressed by MCL cells, has been studied both in combination with existing chemotherapeutic regimens and as monotherapy in the treatment of MCL and this review provides a summary of the main data published to date.

Rituximab monotherapy in the treatment of MCL

Several trials have confirmed that single-agent rituximab has only moderate activity in mantle cell lymphoma (3).

In the largest published study of rituximab monotherapy in MCL, Ghiehmni et al compared the standard rituximab schedule (375mg/m² per week for 4 weeks) with a prolonged schedule (standard schedule followed by additional doses of 375mg/m² given every two months for four doses) in patients with MCL (8). Those who had achieved at least stable disease at week 12 following the standard schedule were randomised to no further treatment (Arm A) or to further doses of rituximab at week 12, month 5, 7 and 9 (Arm B). The primary endpoint was event-free survival (EFS).

At week 12, the RR for the 88 eligible and assessable patients was 27% (95% CI 18-38%; 2.3% CR); the results for the chemotherapy-naïve (RR 27%; 95% CI 13-44%; 3% CR) and the previously-treated patients (RR 28%; 95% CI 17-42%; 2% CR) were similar. A total of 61 were randomised in the second part of the study (27 to Arm A and 34 to Arm B); 27
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did not continue to this part due to either disease progression (n=24) or major toxicity during the induction phase (n=3). After a median follow-up of 29 months, the overall best response (41% of Arm A and 55% of Arm B) and duration of response (15 months in both arms) were not statistically significantly different between the two schedules. The median EFS was 6 months (95% CI 4–14 months) in Arm A and 12 months (95% CI 8–17 months) in Arm B; the difference was not statistically significant. Prolonged treatment did however appear to improve EFS in the subgroup of patients who had been pre-treated (5 months versus 11 months, respectively; p=0.04). The difference between the two groups was statistically significant until 17 months, and it was indistinguishable after this time (8).

Major toxicities in the induction phase included mild infusion-related symptoms; and there were 17 serious adverse events documented. In the randomised phase, grade 3/4 haematological toxicity was observed in 13% of Arm A and 9% in Arm B. There were 6 serious adverse events in Arm A (including two second tumours) and eight in Arm B (including one second tumour, one cardiac death, and one septic shock) (8).

Foran et al conducted a Phase II study in which patients with newly diagnosed MCL (n=34) and previously treated MCL (n=40) were administered rituximab 375mg/m² once weekly for four weeks (9). The response rates were 38% and 37%, respectively, and 10 patients achieved a CR. At a median follow-up from treatment of 1.3 years, the projected median duration of response was 1.2 years (this did not statistically significantly differ depending on previous treatment, and whether a PR or CR was achieved). There were 31 episodes of infection (13 grade 3/4) in follow-up; the most common site was the respiratory tract. Infusion reactions were common but generally mild in nature and limited to the first infusion. Ten patients developed arrhythmias; most noted with the infusions or shortly afterwards (9).

Other studies of rituximab monotherapy are available; all demonstrate its moderate activity as a single agent in this setting. It does however remain an option for the treatment of patients who have contraindications to systemic chemotherapy or significant comorbidity, due to its safety profile. Responses appear to be similar in both chemotherapy-naive and pre-treated patients.

Rituximab in combination with chemotherapy in the treatment of MCL

• Cochrane systematic review

A Cochrane systematic review on chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin’s lymphoma conducted a subgroup analysis on patients MCL, which included three of the trials discussed in the following text (Lenz, Forstpointner, Herold; n=260) (10).

The calculated hazard ratio for death was 0.60 (95% CI 0.37 to 0.98), which indicated an advantage for the R-chemo group. However, there was heterogeneity among the trials (P=0.07). In a sensitivity analysis that excluded the study by Forstpointner 2004, which included patients who had relapsed and who had refractory disease, the heterogeneity disappeared (P = 0.54), but there was still an overall survival advantage for R-chemo compared with chemotherapy alone, with a pooled hazard ratio for mortality of 0.78 (95% CI = 0.45 to 1.35). Overall, patients treated with R-chemo had statistically significantly more leukocytopenia and fewer patients treated with chemotherapy alone, but there were no evidence of a difference in the frequencies of infections or thrombocytopenia between the groups.

The most commonly used combination regimens employing rituximab in the treatment of MCL are discussed in the following sections. In addition, Table 2 summarises smaller, uncontrolled trials assessing rituximab with other chemotherapy combinations.

• R-CHOP (first-line)

The German Low Grade Lymphoma Study Group (GLSG) conducted a randomised Phase III trial comparing CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) to CHOP plus rituximab (R-CHOP) in the first-line treatment of adults with advanced (Ann Arbor stage III or IV) follicular lymphoma, MCL, or lymphoplasmacytic lymphoma (11). Patients with a poor performance status (ECOG > 2) and those with significantly impaired cardiac, pulmonary, hepatic or renal function were excluded from the trial. Randomisation was carried out according to histology, age and number of risk factors, defined by the IPI. Six cycles of CHOP or CHOP-R were administered, with rituximab where applicable given at a dose of 375mg/m² on day 0 of the respective CHOP course. The primary endpoints of the trial were overall response (OR) and CR. As a subgroup analysis of initial results suggested that a higher response rate in the R-CHOP group was mainly due to the group of patients with MCL, the published results were based on this group (n=122 assessable). The main findings were (11):

- The ORR was 75% with CHOP and 94% with R-CHOP (p=0.0054); respective rates of CR were 7% versus 34% (p=0.00024)
- Time to treatment failure (TTF) was a median of 14 months for CHOP alone and 21 months with R-CHOP (p=0.0131)

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London Cancer New Drugs Group—APC/DTC Briefing
• The median time to initiation of salvage therapy was 22 months after CHOP versus 25 months after R-CHOP (p=0.262)

• There was no difference in the PFS of responding patients according to treatment received

• There were no differences seen in overall survival (OS); the estimated 2-year survival rate was 76.6% (median not reached at 18 months of follow-up)

The main treatment-related adverse effects were haematological, with similar incidences in both arms apart from granulocytopenia which was more common in the R-CHOP arm (83% versus 73% respectively). Non-haematological toxicity (mucositis, infections, nausea/vomiting, diarrhoea, alopecia) was also similar between the two groups. Allergies were only seen in the R-CHOP group (7%) and occurred predominantly after the first infusion (11).

In summary, this trial demonstrated a favourable effect of rituximab in terms of induction therapy; however no benefits on PFS or OS were demonstrated. The authors state how these results “emphasize that MCL remains a therapeutic challenge with a high degree of inherent treatment resistance that is still poorly understood”.

An update to this trial, presented at ASH 2008 (available as abstract only), notes that after a median follow-up of 65 months, median TTF was prolonged from 14 months for CHOP to 28 months for R-CHOP (p=0.0003) and median response duration was prolonged from 18 to 29 months, respectively (p=0.0052) (12). Again, no significant improvement of OS had been observed, with estimated 5-year survival rates of 59% after R-CHOP and 46% after CHOP (p=0.27).

• R-Hyper-CVAD and modified R-hyper-CVAD (first-line)

A non-comparative Phase II trial conducted by the MD Anderson Centre evaluated the effectiveness of rituximab added to the hyper-CVAD regime (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) in the treatment of newly diagnosed patients with aggressive MCL (13). The authors note that four cycles of hyper-CVAD alternating with high doses of methotrexate (MTX) and cytarabine has been shown in a previous trial to be associated with high rates of response (93.5% CR and 36% CR). In this trial they assessed the effect of 6-8 cycles of this regimen (hyper-CVAD for one cycle then high dose MTX and cytarabine for one cycle, etc), with rituximab (375mg/m²) administered on day 1 of each 21-day cycle. A number of prophylactic regimens were administered due to the aggressive nature of the regimen, including G-CSF, antivirals, antifungals, antibiotics and folinic acid rescue therapy following MTX. The primary endpoint was the rate of failure-free survival (FFS), defined as recurrence or progression of disease, death caused by disease or toxic effects, and death caused by treatment-related second malignancies.

A total of 97 patients participated in the trial; the median age was 61 (range 41-80) and 32 were aged above 65. The majority of patients had Ann Arbor stage IV disease (99%), with bone marrow (91%) and GI (88%) involvement. After a median follow up of 40 months, the main findings were as follows (13):

• The FFS rate was 64%; the estimated 3-year FFS rate was 73% in those aged ≤ 65 years and 50% in those aged > 65 years (p=0.02 for difference between age groups)

• The overall rate of CR/unconfirmed CR (uCR) after six cycles was 87% (95% CI 79-93); for those aged ≤ 65 years it was 89% and for those aged > 65 years it was 84% (difference between age groups was not statistically significant)

• The estimated 3-year OS rate was 86% for those aged ≤ 65 years and 74% in those aged > 65 years (P=0.047)

Despite these efficacy findings, the toxicity experienced by patients in this trial was significant. A total of 29% of patients did not complete the intended number of cycles due to toxicity, which was principally haematological. The main adverse effects included thrombocytopenia (grade 4: 2-50% depending on cycle), neutropenia (grade 4: 28-68% depending on cycle), neutropenic fever (13%), and infection (6%). Three patients developed myelodysplasia and one developed acute myelogenous leukaemia (AML). The shorter FFS rate coupled with this toxicity led the authors to recommend that this regimen not be used as standard in patients over the age of 65 years. Randomised trials are needed to prospectively evaluate this treatment in comparison to alternatives (13). Another author suggested that the use of stem cell support after this dose-intense induction therapy may further improve the long-term DFS (14).

Preliminary results of a Phase II trial (SWOG 0213) employing this same regimen for the treatment of newly diagnosed patients (aged under 70 years) with MCL have been published in abstract form (n=49); its main purpose was to determine the 1 year PFS (15). The ORR was 88% (40% CR; 18% unconfirmed CR; 30% PR). After a median follow-up of 1.6 years, the 1-year PFS estimate is
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89% (95% CI 80-98%) and the 1-year OS estimate is 91% (95% CI: 82%–99%). The respective estimates for 2 years are 64% (95% CI: 46%–82%) for PFS and 76% (95% CI: 60%–91%) for OS. The authors do however note similar observations to Romaguera et al - the regimen was found to be toxic, and a continuous pattern of relapse over time is observed.

Another group eliminated the methotrexate and cytarabine from the above regimen in an attempt to reduce the toxicity whilst maintaining adequate efficacy in a small pilot phase II study (16). A total of 22 patients with MCL and ECOG PS of 0-2 were treated first-line with the modified R-hyper-CVAD regimen (rituximab 375mg/m² day 1, cyclophosphamide 300mg/m² BD days 1-3, doxorubicin 25mg/m² days 1-2, vincristine 2mg day 3, dexamethasone 40mg days 1-4) given every 28 days for 4-6 cycles. Supportive therapy included filgrastim, allopurinol, paracetamol and diphenhydramine (prior to rituximab) and co-trimoxazole. Patients who responded (PR, CR or CRu) were then given rituximab maintenance therapy (375mg/m² weekly for 4 weeks, repeated every six months for a total of four courses). The primary endpoint was rate of CR.

The median age of the participants was 63 (range 40-81) years, and the majority (86%) had stage IV disease. The ORR to induction therapy with modified R-hyper-CVAD was 77%, consisting of 14 CRs (64%; 95% CI 44-80%) and 3 PRs (14%; 95% CI 4-32%). After a median follow up of 37 months, the median PFS was 37 months (90% CI 15.5 months – not reached) and the median OS had not been reached. The 2-year PFS and OS rates were 59% (90% CI 40-77%) and 77% (90% CI 56-90%), respectively. There were three progressions during rituximab the maintenance period – this was two out of the three entering maintenance with a PR and only one out of the 13 entering maintenance with a CR.

After observing almost universal grade 3-4 neutropenia despite routine filgrastim in the first several patients, plus two deaths (sepsis and peritonitis), the protocol was suspended and the events analysed. The day 11 vincristine and day 11-14 dexamethasone were removed and the remaining 17 patients enrolled experienced no unexpected toxicities during the induction. During the two years of rituximab maintenance, no grade 4 toxicities and five grade 3 toxicities were observed.

The authors note that the CR rate observed in this trial was superior to that associated with R-CHOP in other studies; however no direct comparison has been made so the superiority of one over the other remains to be confirmed (16). This is the first report of the use of maintenance rituximab after first-line chemoimmunotherapy in MCL; although there is a suggestion from these results that it may prolong PFS (median 37 months), this cannot be confirmed unless it is directly compared to administration of the same induction regimen without the use of maintenance rituximab.

- **Rituximab added to fludarabine, cyclophosphamide and mitoxantrone (relapsed/refractory)**

In a prospective, open-label Phase III study, 147 adults with relapsed or refractory follicular (n=72), mantle cell (n=52) or lymphoplasmocytoid (n=16) lymphoma were randomised to treatment with FCM (fludarabine 25mg/m² daily for days 1-3, cyclophosphamide 200mg/m² daily for days 1-3, and mitoxantrone 8mg/m² on day 1; every 4 weeks for 4 cycles) or FCM-R (as above plus rituximab 375mg/m² on the day prior to the chemotherapy course). Following treatment, those who achieved a CR or PR were again randomised, this time to treatment with two further 4-week courses of rituximab (at three and six months) or to observation only (17).

128 patients were evaluable for response to therapy at the time of publication; their median age was 62.5 years (range 35-80) and all had advanced (stage III or IV) disease prior to randomisation. The ORR was 78% in the R-FCM group (33% CR and 45% PR) and 58% in the FCM group (13% CR and 45% PR); the difference between the two groups was statistically significant (p=0.01). Subgroup analyses according to lymphoma subtype found that R-FCM was superior to FCM for OOR in follicular lymphoma (94% versus 70%; p=0.011) but the difference was not statistically significant for mantle cell lymphoma (58% versus 46%; p=0.282). After a median observation time of 18 months (range 1-43 months), the estimated OS was 63% at 2 years; although the median OS had not been reached at 3 years for the R-FCM group, it was 24 months for those randomised to FCM alone (p=0.003). For MCL, the median OS had not been reached for R-FCM, but it was estimated at 11 months for FCM (p=0.0042). The overall estimated PFS is 16 months for R-FCM versus 10 months with FCM (p=0.0381). For those with MCL, the respective values were 8 months versus 4 months (p=0.3887).

The main treatment-related toxicity was myelosuppression, and granulocytopenia in particular (grade 3 or 4 in 40% of cycles with comparable incidence in both treatment groups). Grade 3/4 lymphocytopenia was more common in the R-FCM group (51% versus 39% of FCM courses; p=0.006; there was however no increased risk of infectious complications) (17).

Results from the rituximab maintenance phase of the study were later reported separately (18). Due to the advantage seen for R-FCM over FCM alone...
Rituximab for Mantle Cell Lymphoma

(as above), further randomisation was stopped after 147 patients; all subsequent patients received R-FCM. A total of 195 patients were randomised to receive either no further therapy or maintenance rituximab, and 176 of these were evaluable (138 of these had received R-FMC in the initial part of the study, as above). After a median follow-up of 26 months, the median PFS after end of induction had not been reached in the R-maintenance arm compared to 17 months in patients who received no further treatment (p<0.001). When restricting the analysis to those who had initially received R-FCM and to those with mantle cell lymphoma, the median PFS values were 14 months versus 12 months, respectively (p=0.049). A higher proportion of the maintenance group experienced ongoing remission compared to those with no further treatment (p=0.10). The rate of serious infections was 57% in the group versus 57% in the group with no further treatment (p<0.001). When restricting the analysis to those who had initially received R-FCM and to those with mantle cell lymphoma, the estimated two-year EFS was 69% for R-MCP versus 85.5% and 42% in the R-MCP arm versus 65.5% and 20% in the MCP arm (p<0.0001). Separate results are only presented for follicular lymphoma in the abstract; no specific results for the mantle cell population are detailed. In the overall group, median EFS was 19 months for both groups. The response criteria used included EFS (intention-to-treat), OS (intention-to-treat), PFS (calculated for all responding patients who completed the treatment program), and molecular remission duration.

Whether the addition of rituximab to myeloablative regimes further improves treatment is the issue in question. Promising results have been seen when it has been incorporated after autoSCT, during induction or mobilisation treatment (i.e. ‘in vivo purging’) (3).

In the second Phase II Nordic MCL study (MCL-2), a total of 160 consecutive untreated patients (age range 32-65 years; median 56 years) with newly-diagnosed stage II to IV MCL (84% stage IV) were treated with the following (33):

- **Induction:** six cycles - Maxi-CHOP x 3 alternating with high-dose (HD)-cytarabine x 2; rituximab on first day of cycles 4 and 5
- **Stem cell mobilisation:** HD-cytarabine (plus G-CSF) with rituximab on day 1 and 9
- **Stem cell purging:** four doses of rituximab (as already stated above)
- **High-dose therapy following stem cell harvest:** BEAM (n=90) or BEAC (n=55), followed 1-2 weeks later by stem cell infusion (autoSCT; if this was delayed for logistical reasons then 1-2 cycles of immunochemotherapy (R-maxi-CHOP or R-cytarabine) was permitted
- **Pre-emptive treatment at molecular relapse:** rituximab 375mg/m² weekly for 4 weeks

The response criteria used included EFS (intention-to-treat), OS (intention-to-treat), PFS (calculated for all responding patients who completed the treatment program), and molecular remission duration.

The results were compared to historical controls – consisting of 41 similar patients who took part in the first Nordic MCL study (MCL-1), who received 4 cycles of Maxi-CHOP without rituximab before BEAM or BEAC and autoSCT (in-vitro stem cell purging). The main difference between the two trials was therefore the addition of rituximab and HD cytarabine in MCL-2.

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**Rituximab and stem cell transplantation**

Younger MCL patients without significant co-morbidity should be treated aggressively, and myeloablative chemotherapy followed by autologous SCT represents one of the standard first-line therapeutic options in the treatment of such patients (3). High overall and complete response rates are also reported when high-dose chemotherapy regimens are used in these patients at first remission. However relapse is the main concern and the impact on overall survival remains unclear (7).
With a median follow-up of 3.8 years, the main findings were as follows (33):

- The 4-year EFS rate was 63% - this compares to 18% in the MCL-1 trial (p<0.001), and the difference was mainly due to a reduction in the rate of events caused by lymphoma from 76% in MCL-1 to 37.5% in MCL-2.
- The 4-year OS was 81%, compared to 55% in MCL-1 (p=0.002)
- Following induction treatment, the overall response rate was 96% (154 patients), including 45.6% with a complete response (CR), 8.8% with an unconfirmed CR, and 41.9% with a partial response (PR). This compares to an ORR of 76% (p=0.001) and a 27% CR (p<0.001) in MCL-1.
- A total of 145 responders went on to high-dose therapy, of which 130 (89.7%) had a CR; 7.6% remained in partial response and 4 (2.8%) had died or progressed. At assessment of molecular response to months after high-dose therapy, 73 (92%) were PCR-negative compared to 38% in the MCL-1 trial (p<0.001)
- During follow-up, a total of 40 patients had relapsed or progressed, with a 4-year PFS of 73%; this is higher than the corresponding 37% seen in MCL-1 (p=0.001).
- 26 patients received re-treatment with rituximab, with a median molecular and clinical remission duration of 15 and 19 months, respectively.

Of the 465 cycles of maxi-CHOP and 464 cycles of high-dose cytarabine, 17% and 12%, respectively, led to hospitalisation for grade 3 or 4 adverse events, and 80% of these were neutropenic fever. Five of the 15 patients who failed to proceed to high-dose therapy did so because of toxicity, including three with recurrent, severe infection.

The authors note the findings of Romaguera et al (discussed earlier; 12) and how both their R-Hyper-CVAD/MTX/cytarabine regimen and the MCL-2 protocol – both containing the CHOP components, high-dose cytarabine and rituximab – appear to result in similar response rates. The important difference between these two regimens is that the omission of high-dose therapy after the R-Hyper-CVAD/MTX/cytarabine regimen allows the inclusion of older patients – however a continuous pattern of relapse was observed, in comparison to the MCL-2 results which showed emerging plateaus in both EFS and PFS. A randomised trial is required to confirm whether high-dose therapy is required after this more intensive induction therapy (33).

Of note, although rituximab re-treatment re-induced molecular remission- in the majority of patients treated, no PFS advantage was demonstrated and further data in this area is required. A randomised study has suggested that rituximab maintenance may prolong second CR (Forstpointner et al; ref 17 discussed earlier) and other randomised studies in this area are currently ongoing (33).

In the trial by Lenz et al, comparing induction therapy with CHOP versus R-CHOP (as discussed earlier), those aged ≤ 65 years who achieved a CR or PR were randomised to either myeloablative radiochemotherapy followed by autoSCT (n=23; 14 after R-CHOP and 9 after CHOP) or maintenance therapy with interferon alfa (n=62; 35 R-CHOP and 27 CHOP) (11). There was no statistically significant difference in PFS between CHOP and R-CHOP for either the autoSCT group or the interferon alfa maintenance group; although patient numbers were small this suggests that the favourable effects of rituximab may be limited to the induction period (11).

Other small non-randomised studies of rituximab in the setting of SCT have been published; these include (brief details only):

- Mangel et al compared the outcome of 20 patients with newly diagnosed MCL treated on a prospective trial of autoSCT and rituximab immunotherapy with that of 40 matched historical control patients treated with standard combination chemotherapy (anthracycline- or cyclophosphamide-fludarabine-based), identified from a lymphoma database. PFS at 3 years was superior in patients treated with autoSCT-rituximab compared with those treated with conventional chemotherapy (89% versus 29%, P <0.00001); OS results were borderline (88% versus 65%, P = 0.052) (34).
- De Guilbert et al reported on a series of 24 patients with newly diagnosed MCL treated with 4-6 courses of DHAP-rituximab followed by auto-SCT for patients <65 years. 3-year OS and EFS rates were 69% and 65% respectively, for the 24 patients. In an intention-to-treat analysis, respective values were 75% and 76% for the 17 patients aged < 65 years old (35).
- In a Phase II trial, Dreger et al treated 34 patients with newly diagnosed MCL with a sequential dose-escalating therapy comprising standard chemotherapy for remission induction,
intensive ara-C-containing chemotherapy for mobilisation of stem cells, and myeloablative therapy (total body irradiation and high-dose cyclophosphamide supplemented with two doses of rituximab) followed by auto-SCT. Outcomes were compared with those of 34 historical controls treated identically but without rituximab. EFS was increased with rituximab (not reached vs. 43 months; hazard ratio 0.38; p=0.036), however there were no differences in terms of engraftment, toxicity or clinical response (36).

- Ritchie et al performed a study of hyper-CVAD plus rituximab, followed by autoSCT with high-dose busulfan and melphalan conditioning, in patients with responsive disease. Thirteen MCL patients (median age of 54) were treated; CR was achieved in 12 patients (92%) after hyper-CVAD + R and 12 completed auto-SCT after conditioning. With a median follow-up from diagnosis of 36 months, the observed OS and EFS were both 92% for the whole cohort (37).

- Thieblemont et al retrospectively evaluated the efficacy of chemotherapy combined with rituximab followed by high-dose therapy (HDT) plus auto-SCT in 34 patients with MCL, including 29 (85%) treated first-line. Rituximab was administered as 4 injections prior to harvest in 25 patients (73%) or simultaneously with chemotherapy in 9 patients (27%). Following induction therapy, all patients but one had a response, including 14 (41%) CR and 19 (56%) PR. Three months following transplantation, 24 patients (71%) were in CR, and 7 patients (21%) were in PR. The estimated OS 3 years following transplantation was 87%. With a median follow-up of 2.6 years, the estimated median time to disease progression was 3.4 years (38).

Discussion points/Issues for consideration

- There have been a number of trials of varying quality assessing the addition of rituximab to chemotherapy regimens in the treatment of MCL. Three of these are Phase III trials (one available in abstract form only) - assessing rituximab added to CHOP (first-line), MCP (first-line), and FCM (relapsed/refractory).

- The only Phase III trial to exclusively enrol patients with MCL was that comparing CHOP to R-CHOP as induction treatment; this found that addition of rituximab improved the ORR and lengthened time to treatment failure, but there was no observed improvement in progression-free or overall survival.

- The Phase III trial evaluating rituximab added to FCM versus FCM alone in advanced, pre-treated disease looked at different lymphomas; 35% were MCL. R-FCM was associated with a higher ORR compared to FCM alone, but this was not statistically significant. The use of rituximab maintenance in the MCL patients resulted in a 2-month improvement in PFS but this was of borderline significance. The study was not powered to detect differences in outcomes for each separate subgroup of lymphoma.

- The study evaluating the addition of rituximab to MCP also included a number of lymphoma types; the study has been reported in abstract form only and did not present results for the MCL subgroup.

- In general, the ORR when rituximab is added to chemotherapy in MCL is lower than that observed for other B-cell lymphomas (e.g. follicular lymphoma); this reflects the generally lower response to treatment overall in this subgroup.

- The recently published Phase II trial from the Nordic Lymphoma Group appears to be the most promising in terms of use of rituximab around auto-SCT – when compared to a historical group who received no rituximab (and also no high-dose cytarabine), the EFS, OS and PFS were increased. Further studies directly comparing such regimens with or without rituximab (rather than comparison with historical controls) are desirable.
Table 2: Uncontrolled studies evaluating rituximab in combination with chemotherapy for the treatment of MCL

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen*</th>
<th>Patient type and number</th>
<th>Main treatment outcomes</th>
<th>Haematological toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauwens D et al (2005) (20)</td>
<td>Chlorambucil plus rituximab</td>
<td>N=14, MCL not eligible for aggressive therapy; 2 had no prior treatment</td>
<td>ORR 64% (95% CI 39-84), with five (36%) CR and four (29%) PR. PFS 26 mo (95% CI 4-48) for responders and 15 mo (95% CI &lt;1-33) for all pts. 2-year survival: 58%</td>
<td>Five patients (36%) did not complete therapy due to toxicity. Grade 3/4 neutropenia in 36%, and thrombocytopenia in 21%; grade 3 infection in 29%.</td>
</tr>
<tr>
<td>Drach J et al (2006) (21)</td>
<td>Rituximab plus bortezomib and dexamethasone (BORID) (6 cycles)</td>
<td>Relapsed/refractory MCL; n=14 (12 evaluable)</td>
<td>ORR in 9 pts (3 CR and 6 PR), and 2 pts experienced stable disease. All pts with CR were progression-free at 12 mo; 3 with PR were progression-free at 6 mo.</td>
<td>Five grade 3/4 infections; thrombocytopenia in 2 pts</td>
</tr>
<tr>
<td>Inwards DJ et al (2006) (22)</td>
<td>Rituximab and cladribine (2-6 cycles)</td>
<td>Previously untreated MCL; n=29</td>
<td>15 had a CR (51.7%; 95% CI: 32.5–70.6%); and 4 a PR. After median follow-up 14.3 mo, 26 (89.7%) were alive and 1-yr survival rate was 89.3% (95% CI: 78.5–100)</td>
<td>Grade 4 neutropenia in 24.1% and leucopenia in 6.9%</td>
</tr>
<tr>
<td>Jermann M et al (23)</td>
<td>Rituximab + EPOCH as salvage therapy</td>
<td>N=50 (B-cell lymphomas; 7 MCL); relapsed/refractory</td>
<td>Median follow-up of 33 mo ORR (all pts) 88%; 28% CR and 40% PR. Median event-free survival: 15 mo in MCL pts and 11.8 mo overall</td>
<td>Febrile neutropenia in 13 of 181 cycles (7%); grade 3 CR and 40% PR. Median OS not reached; estimated 3yr OS 75%</td>
</tr>
<tr>
<td>Kaufmann H et al (24)</td>
<td>Rituximab plus thalidomide</td>
<td>Relapsed/refractory MCL; N=16 (all previous CHOP or CHOP-like regimen)</td>
<td>ORR in 13 pts (81%; 95% CI 60-103%), with 5 CR (31%; 95% CI 5.7-56.8%). Median PFS 20.4 mo (95% CI 17.6-23.6 mo). Median OS not reached; estimated 3yr OS 75%</td>
<td>Grade IV neutropenia in one pt</td>
</tr>
<tr>
<td>Robak T et al (25)</td>
<td>Rituximab plus cladribine (RC) or RC + cyclophosphamide (RCC)</td>
<td>N=54; including 9 with MCL (recurrent/refractory)</td>
<td>MCL ORR 67%, with 2 CR (22%); no statistically significant differences between RC and RCC (small sample)</td>
<td>Grade 3/4 neutropenia in 11%, 11 episodes (20%) of Grade 3/4 infections, Grade 3 anaemia in 7% and grade 3/4 thrombocytopenia in 7%.</td>
</tr>
<tr>
<td>Rodriguez J et al (26)</td>
<td>Rituximab with gemcitabine and oxaliplatin</td>
<td>Relapsed/refractory MCL; n=14</td>
<td>ORR 85%; CR in 9 pts (64%) and PR in 3 (21%). At median follow-up of 11 mo, PFS 45% and OS 58% at 12 months</td>
<td>Grade 3/4 neutropenia in 14%, thrombocytopenia in 36%; no grade 3/4 anaemia or infection</td>
</tr>
<tr>
<td>Rummel MJ et al (27)</td>
<td>Rituximab and bendamustine (4 cycles)</td>
<td>Total n=63; 16 (25%) had MCL; all patients had relapsed and 7 were refractory</td>
<td>MCL pts: ORR 75% (95% CI 48-93%) and CR 50%. Median PFS 18 mo (range 6-22+ months)</td>
<td>All pts: Grade 3/4 leukopenia in 16% of cycles, thrombocytopenia in 3% and anaemia in 1%.</td>
</tr>
<tr>
<td>Tam CS et al (28)</td>
<td>Fludarabine, cyclophosphamide and rituximab (FCR)</td>
<td>N=77 (indolent B-cell proliferative disorders) 8 MCL (one previously untreated)</td>
<td>MCL pts: ORR 38% (all CR) Entire cohort: ORR 83% (42% CR) Median of 20 mo follow-up, 3yr PFS 48% and 3yr OS 72%</td>
<td>Grade 3/4 neutropenia in 33% (with severe sepsis in 9% of cycles), thrombocytopenia 4%, infection 9.5%</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Regimen</td>
<td>Patient Details</td>
<td>Results</td>
<td>Adverse Events</td>
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<tr>
<td>Thomas DW et al (29)</td>
<td>Fludarabine and cyclophosphamide (FC) +/- rituximab</td>
<td>N=16; all had received prior CHOP therapy; 8 received FCR</td>
<td>ORR 75% (62.5% with FC and 87.5% with FCR); median duration of response of 11 mo (4-25+ mo)</td>
<td>Grade 3/4 neutropenia in 3 pts; grade 3 thrombocytopenia in 2 pts</td>
</tr>
<tr>
<td>Wang M et al (30)</td>
<td>Rituximab plus lenalidomide</td>
<td>N=18 MCL, 1-4 previous lines of therapy (Phase I/II; phase II part ongoing)</td>
<td>Ten pts taking 20mg (minimum therapeutic dose) evaluable for response; ORR 70% including 3 CR (30%) and 4 PR (40%)</td>
<td>Grade 3 neutropenia (n=11), febrile neutropenia (n=2), and thrombocytopenia (n=2); Grade 4 neutropenia (n=5)</td>
</tr>
<tr>
<td>Weide R et al (31)</td>
<td>Bendamustine, mitoxantrone, rituximab (4 cycles)</td>
<td>N=57 relapsed/refractory indolent lymphomas or MCL (n=18 MCL)</td>
<td>MCL pts: ORR 77%; 6 CR (33%), 8 PR (44%) After median 27 months follow-up, estimated median PFS 21 months and 2 yr survival 60%</td>
<td>Grade 3/4 anaemia in 10%, leukocytopenia 78%, granulocytopenia 46%, thrombocytopenia 16%, grade 3 infection 4%</td>
</tr>
<tr>
<td>Williams ME et al (32)</td>
<td>Rituximab and bendamustine (4-6 cycles)</td>
<td>57 evaluable pts with B-cell lymphomas (n=9 MCL)</td>
<td>MCL pts: ORR 89% (CR 33%). For all pts, median duration of response and PFS not reached after a median follow-up of 3.7 mo</td>
<td>Primary grade 3/4 haematological toxicity was neutropenia (29%), with 1 event of sepsis</td>
</tr>
</tbody>
</table>

*Please refer to full text articles for further details of the regimens
EPOCH: etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin

The document reflects the views of LCNDG and may not reflect those of the reviewers
References:

29. Thomas DW et al (2005) Superior quality and duration of responses among patients with mantle-cell lymphoma treated with fludarabine and cyclophosphamide with or without rituximab compared with prior responses to CHOP. Leuk Lymph; 46 (4):549-552