Published in final edited form as:

Am J Hematol. 2015 June ; 90(6): E111–E116. doi:10.1002/ajh.23996.

Updated survival analysis of two sequential prospective trials of R-MACLO-IVAM followed by maintenance for newly diagnosed mantle cell lymphoma

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Abstract

A phase II trial of R-MACLO-IVAM followed by thalidomide maintenance for mantle cell lymphoma (MCL) demonstrated promising progression-free survival (PFS) and overall survival (OS) rates. Thalidomide maintenance was associated with significant toxicity and was subsequently modified to rituximab maintenance. Herein we present updated results and follow-up. Two sequential phase II trials included chemotherapy-naïve patients with MCL up to 75 years old. Four cycles of R-MACLO-IVAM chemotherapy were delivered as previously described. Patients who achieved complete responses (CR) were eligible for thalidomide or rituximab maintenance therapy. Among 36 patients enrolled, the mantle cell lymphoma International Prognostic Index (MIPI) was low in 53%, intermediate in 36% and high in 11%. Thirty-five patients completed at least 2 cycles of chemotherapy; 34 (94%) achieved a CR. After a median follow-up of 74.4 months, the 5-year PFS was 51% (95% CI 33% – 68%) and the 5-year OS was 85% (95% CI 73% – 97%). Two deaths occurred during the chemotherapy phase due to disease progression and neutropenic sepsis respectively. One patient developed secondary acute myeloid

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CONFLICT OF INTEREST STATEMENT

The authors report no potential conflicts of interest.

AUTHORSHIP AND DISCLOSURES

ISL was the principal investigator and takes primary responsibility for the paper; designed the study. PJH, DG, JH, AS, JDR and ISL recruited and treated the patients; PJH, JDS, AGA, IR and ISL collected and analyzed the data; PJH and ISL wrote the manuscript.

leukemia after 7 years. R-MACLO-IVAM chemotherapy is effective for patients with newly diagnosed MCL.

INTRODUCTION

Mantle cell lymphoma (MCL) is an unfavorable subtype of non-Hodgkin lymphoma characterized by the t(11,14) which results in overexpression of the cell cycle regulator cyclin D1[1]. This can lead to a tumor characterized by high proliferation and an aggressive disease course in many cases. Although most patients demonstrate an initial response to chemotherapy, relapses are common and cure remains an elusive goal. Contemporary treatment for younger patients with MCL consists of augmented doses of CHOP-like chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) combined with high-dose cytarabine. In the United States, a popular regimen is Hyper-CVAD/MA (cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine) for 6–8 cycles. The initial study reported by Khouri *et al* also included autologous stem cell transplantation (ASCT) as consolidation, leading to a complete remission (CR) rate of 94% and a 3-year overall survival (OS) and event-free survival (EFS) of 92% and 72%, respectively[2]. Addition of rituximab to this regimen without ASCT as consolidation resulted in a CR rate of 87% and a 3-year OS and EFS of 82% and 64% respectively[3]. These outcomes represented a marked improvement compared to results reported with CHOP with or without rituximab[4–6].

In Europe, the Nordic Lymphoma group MCL2 study utilized rituximab with an augmented CHOP-like regimen called maxi-CHOP alternating with high-dose cytarabine, followed by ASCT and this therapy resulted in an ORR of 96% and a 6-year EFS and OS of 56% and 70% respectively[7]. The French adult lymphoma study group (GELA) also reported similar results with rituximab plus CHOP and DHAP (dexamethasone, cytarabine and cisplatin) followed by ASCT[8]. The ORR was 95% and the 5-year OS rate was 75%. However, all these therapies were associated with a continuous pattern of relapses and the survival curves did not achieve a plateau with extended follow-up. In order to prevent late relapses, maintenance therapy has been tested. The largest study randomized elderly patients with MCL to rituximab versus interferon alfa maintenance after initial therapy with R-CHOP[9]. Among patients who had a response to R-CHOP, maintenance therapy with rituximab significantly improved survival (4-year OS rate, 87%, vs. 63% with interferon alfa; $P = 0.005$). Since thalidomide and lenalidomide have shown activity against MCL[10, 11], these oral agents are also attractive options for maintenance therapy.

Lossos *et al* reported results of a phase II trial testing the hypothesis that intensive induction therapy with R-MACLO-IVAM (rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, ifosfamide, cytarabine and etoposide) followed by maintenance thalidomide may improve response rates and survival in MCL[12]. The preliminary results of this trial were promising but thalidomide maintenance resulted in significant toxicity. Therefore, a second phase II study was initiated testing a similar intensive induction regimen with rituximab maintenance instead of thalidomide. The combined results of these two studies are reported herein.

METHODS

Study Design and Objectives

Two sequential single-arm, open label prospective phase II clinical trials of R-MACLO-IVAM in chemotherapy naive patients with MCL were conducted. The study design has been previously described[12]. The primary endpoint was progression-free survival (PFS), defined as the time from start of study treatment to documented evidence of disease relapse or death from any cause. Secondary endpoints included safety and OS. The first study (UM-MCL1) was registered at ClinicalTrials.gov under the identifier NCT00450801, and second (UM-MCL2) was NCT00878254.

Eligibility

The eligibility criteria have been previously described[12]. Briefly, untreated patients with a histologically confirmed MCL diagnosis between the ages of 18 and 75 years, clinical stage III or IV disease, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 and adequate organ function were eligible. Patients were excluded if they had any prior chemotherapy, immunotherapy or radiotherapy or if their disease involved the central nervous system. Only patients whose specimens fulfilled the diagnostic WHO criteria for MCL[13], with overexpression of cyclin D1 or presence of t(11;14), were included.

Pretreatment Investigations

Baseline evaluation included a complete medical history and physical examination with assessment of ECOG PS, routine blood tests in addition to lactate dehydrogenase (LDH), beta-2 microglobulin, hepatitis B, C and HIV serology. Bone marrow aspiration and biopsy were performed and contrast-enhanced computed tomography (CT) of the neck, chest, abdomen and pelvis were obtained. All patients underwent baseline colonoscopy with biopsies of any abnormal areas or random biopsies if the inspection was normal. Cardiac function was assessed by electrocardiography in all patients and an echocardiogram or a cardiac Multi Gated Acquisition (MUGA) scan. Positron emission tomography / computed tomography (PET/CT) was optional. Patients were staged according to the Ann Arbor system[14].

Treatment

The study schema has been previously described in detail[12]. Cycle 1 consisted of R-MACLO (rituximab, methotrexate, doxorubicin, cyclophosphamide and vincristine) followed by G-CSF. When the absolute neutrophil count (ANC) was $>1.5 \times 10^9/L$, cycle 2 with R-IVAM (rituximab, ifosfamide, mesna, etoposide and cytarabine) was begun, followed by G-CSF. After recovery from cycle 2, patients had re-evaluation with CT (PET was optional) prior to re-hospitalization. Two weeks after ANC recovery from cycle 2, cycles 3 and 4 were given in identical fashion to 1 and 2. Four weeks after ANC recovery from cycle 4, patients were reevaluated with CT (or PET/CT). Patients with bone marrow and/or gastrointestinal involvement at baseline were required to have a repeat bone marrow examination and/or colonoscopy, respectively, to evaluate response to treatment. Patients who achieved a complete response (CR) at the end of therapy started treatment with aspirin

81mg/day and maintenance thalidomide 200 mg/day until MCL relapse or intolerable toxicity.

In the UM-MCL2 study, the dose of methotrexate in cycles 1 and 3 was reduced from 5.52 g/m² to 3 g/m² and the maintenance therapy for patients achieving a CR was changed to rituximab 375mg/m² weekly for 4 weeks, every 6 months for 3 years. Response was assessed after the second cycle, at the end of treatment, and then every 3 months for a minimum of 3 years until death or disease progression. Patients in remission continued to be followed up after 3 years at 6 month intervals until 5 years and evaluated with repeated CT and then yearly thereafter. Response and progression were based on International Working Group Response Criteria for NHL[15].

Statistical Methods

Both the UM-MCL1 and UM-MCL2 studies had a study size of 22 patients based on the precision of a two-sided 95% confidence interval (CI) for the 18-month PFS rate and an expected enrollment of 6 patients per year over a 3½ year period. This was based on the hypothesis that study treatment would achieve a median PFS of 18 months and Peto's approximation for the standard error of a Kaplan-Meier estimate was applied[16]. Assuming no losses to follow up, an 18-month PFS rate of 50% observed in 22 patients would have standard error of approximately 11%. This report represents a planned interim analysis after at least 50% of the planned accrual on the UM-MCL2 study was achieved with sufficient follow-up.

PFS was calculated from the date of the start of chemotherapy to the date of disease progression, relapse or death from any cause. Patients known to be alive and without progressive disease were censored at the time of last contact. OS was calculated from the date of the start of chemotherapy to the date of death from any cause or last contact. PFS and OS were estimated by the Kaplan-Meier method with corresponding 2-sided 95% CI's for survival proportions based on Greenwood's variance and the log-transform method[17]. Severity of adverse events was determined using Common Terminology Criteria for Adverse Events version 4.0 [18].

RESULTS

Patient Disposition And Characteristics

There were 36 patients with newly diagnosed, untreated MCL enrolled between 2004 and 2013. All patients were evaluable for toxicity, response and survival. Table 1 shows the baseline characteristics of the 36 patients. The median age was 56.6 years (range 39–73) and 94% had an ECOG PS of 0 or 1. All patients had at least stage III disease, with bone marrow involvement in 83% and gastrointestinal involvement in 50%. Six patients (17%) had a pleural effusion and/or parenchymal lung involvement at the time of diagnosis. Thirty-two patients (89%) had the diffuse variant and the remaining 4 patients had the blastic variant of MCL. The distribution according to MCL international prognostic index (MIPI) risk groups[19] was 53%, 36% and 11% for low, intermediate and high risk groups, respectively. Nineteen patients (53%) had a beta-2 microglobulin > 3 mg/dl. Data on Ki-67 staining was

available for 26 patients and the median staining was 44% (range 5–90%) and > 30% in 15 patients.

Efficacy

Thirty-one patients completed all 4 cycles of therapy. Among the five patients who did not complete 4 cycles, one patient died during cycle 1 due to disease progression, treatment was stopped after cycle 2 in another patient due to an empyema, and after third cycle in 3 other patients due to delayed recovery of their blood counts. Methotrexate was omitted from the first cycle in 5 patients because of uncontrolled pleural effusion. Among the 35 patients who completed at least 2 cycles of therapy, 34 achieved a CR (97%; 95% CI, 85 to 100%).

The median follow-up was 74.4 months. The Kaplan-Meier PFS and OS plots are shown in Figures 1A and 1B respectively. The median PFS was 88 months (95% CI 40.4 – 135.6 months) and the median OS has not been reached. The estimated 5-year PFS and OS rates were 51% (95% CI 33% – 68%) and 85% (95% CI 73% – 97%) respectively. The MIPI score was a statistically significant prognostic factor for both PFS and OS, as shown in Figures 1C and 1D respectively. There was no significant PFS or OS difference between low and intermediate MIPI risk groups, but the high MIPI risk group had significantly worse PFS and OS compared to the low and intermediate risk groups.

To date, there have been 14 relapses and 9 deaths. Two deaths occurred during the chemotherapy phase - one within 7 days of starting cycle 1 due to progressive disease, and one during recovery from cycle 4 due to sepsis. Two patients died from second malignancies (non-small cell lung cancer and acute myeloid leukemia) while still in remission from MCL, and five died due to relapsed MCL. Treatment administered at the time of relapse included rituximab/bendamustine in 8 patients, ibrutinib in 2 patients, radioimmunotherapy with ibritumomab in 2 patients and no therapy in one patient. One patient underwent an allogeneic stem cell transplant after successful salvage therapy with rituximab/bendamustine.

Maintenance therapy

Twenty-two patients were eligible for thalidomide maintenance; one patient died prior to this phase and one never started thalidomide due to preexisting severe peripheral neuropathy. Among the 20 patients who initiated thalidomide maintenance, the median duration of use was 9.6 months (range 0.2 to 111 months). Three patients remain on thalidomide after 111, 87 and 79 months respectively, one discontinued therapy due to disease relapse and 16 discontinued due to toxicity. There was a trend towards longer PFS in patients with longer exposure to thalidomide but this did not achieve statistical significance.

Among the 14 patients eligible for rituximab maintenance, 3 never initiated it as a result of early relapse, death and failure to achieve a complete response respectively. For those who received rituximab maintenance, the median duration of maintenance was 34 months; 6 patients completed the 6 prescribed courses, 4 patients are still receiving therapy, and 1 patient was taken off therapy after 4 cycles due to disease relapse.

Toxicity—The most common hematological and non-hematological toxicities of the chemotherapy phase are summarized in Table 2. Grade 3–4 neutropenia, anemia and thrombocytopenia were seen in 54%, 37% and 34% of R-MACLO cycles, respectively, and in 56%, 71% and 85% of R-IVAM cycles, respectively. During the entire course of therapy, patients received a median of 9 units of packed red blood cells (range 3 to 26) and 9 doses of platelets (range 1 to 16). The median duration of grade III or greater neutropenia was 3 days for R-MACLO cycles and 8 days for R-IVAM cycles. Bacteremia and febrile neutropenia was a complication of 20 (15%) and 44 (32%) cycles of R-MACLO and R-IVAM, respectively. Six episodes of reversible grade 1 or 2 renal toxicity occurred after methotrexate among the first 22 treated patients. This resulted in dose modification of methotrexate from 5.52 g/m² to 3 g/m² in the 14 patients in the UM-MCL2 study. Despite this dose reduction, 4 of these 14 patients still developed grade 1 or 2 renal toxicity and one developed grade 3 toxicity, all of which were reversible. Aside from nephrotoxicity, there were no appreciable differences in the toxicities in the UM-MCL1 and the UM-MCL2 studies.

The most common adverse events noted during thalidomide maintenance were neutropenia and peripheral neuropathy. Among the 16 patients who discontinued thalidomide due to toxicity, 7 (35%) experienced grade 3–4 neutropenia and 8 (40%) had grade 3–4 peripheral neuropathy. Four patients (20%) were diagnosed with malignancies while on thalidomide - 2 renal cell carcinomas (RCC), 1 non-small cell lung cancer and 1 prostate cancer. These cancers were detected at 9, 33, 27 and 74 months after MCL diagnosis respectively. The patient who was diagnosed at 9 months with RCC had the lesion present in retrospect (but undiagnosed) at the time of MCL diagnosis so it did not represent a true secondary malignancy. One patient, who never started thalidomide due to delayed recovery of the blood counts, developed acute myeloid leukemia (AML) 7 years after the diagnosis of MCL. This was considered to be therapy-related AML since the karyotype was complex, and the patient was being worked up for an allogeneic SCT at the time of this report. There were no significant adverse events attributed to rituximab in the patients who received rituximab maintenance.

DISCUSSION

The frontline treatment for young patients with MCL has now evolved to include intensified CHOP-like chemotherapy sequenced with high-dose cytarabine with or without consolidation with ASCT. The rituximab-hyper-CVAD/MA regimen has been validated in a multicenter setting and is a popular regimen in the USA[20]. Recent European trials have used similar chemotherapy regimens followed by ASCT[7, 8, 21–23]. Intensifying induction and adding maintenance have been tested as methods of preventing late relapses, but all the North American and European regimens are still associated with relapses after 5 years.

The response rate observed in the present study is high, and is typical of contemporary regimens that contain high-dose cytarabine. With mature follow-up, the relapse rate and survival seen in this study compares favorably with other standard regimens that include ASCT as shown in Table 3. Although the present study is smaller than the other listed studies, the distribution of MIPI scores among these studies are similar to our study. Of note,

the French study by Delarue et al[8] excluded patients with blastic MCL while our study contained 11% with blastic MCL and the responses to therapy were indistinguishable from patients with diffuse variant. The wide discrepancy observed in our study between the 5-year PFS and OS (51% versus 85%) is likely due to the emergence of more effective salvage regimens for patients with relapsed MCL, including bendamustine and ibrutinib. Only one patient in our study underwent a stem cell transplant (allogeneic) to consolidate a second remission.

The efficacy seen with this induction regimen came at the cost of one toxic death and one case of secondary AML. The myelosuppression seen during recovery from each cycle was substantial and required meticulous supportive care. Patients remained hospitalized for the majority of the 3-month induction chemotherapy phase. Despite the modification of the protocol to reduce the dose of methotrexate for the UM-MCL2 study, there was still nephrotoxicity seen (27% in the first study vs 36% in the second), but these were all reversible. Although the toxicities appeared to be considerable, the rate of myelosuppression and secondary AML are comparable to the Hyper-CVAD/MA regimen, with reported rates of secondary MDS/AML of 4% [2, 3]. Furthermore, the mortality associated with our regimen (one patient) was not different from the 2–6% mortality rate reported with the Hyper-CVAD/MA regimen. One potential advantage of the R-MACLO-IVAM regimen is the shorter duration compared to Hyper-CVAD/MA (3 months versus 5–6 months). Furthermore, the present study included patients up to 75 years of age, and we did not observe worse survival for patients older than 65 years old (Supplementary figure 2) in contrast to the Hyper-CVAD/MA regimen which performed poorly in patients over 65 years [2, 3, 20].

Thalidomide maintenance could not be tolerated by most patients at the starting dose of 200mg daily, and most of the discontinuations were due to peripheral neuropathy and/or neutropenia. The 3 patients who remained on thalidomide for over 7 years all had dose reductions to 100mg daily. Despite the toxicity, there appeared to be a trend towards benefit for prolonged exposure to thalidomide. The duration of follow-up for the patients who received rituximab maintenance was too short to demonstrate any benefit at this point (Supplementary Figure 1). However, rituximab maintenance was clearly shown to have an overall survival benefit in European MCL network study for patients who were treated with R-CHOP, and an event-free survival benefit in the recently presented LyMa trial [9, 23].

Since it appears that we have reached the ceiling with regards to response rates during induction for MCL, maintenance therapy, or post-induction consolidation seems to be the area where most improvement is needed. Among the experts in the field there are currently active discussions on the benefit of consolidation with stem cell transplantation and this approach remains controversial. Optimizing maintenance may be a less toxic alternative. An unanswered question about maintenance therapy is whether a fixed duration (such as 3 years) is sufficient, or if maintenance should be continued indefinitely. Given the continuous pattern of relapses seen in most MCL studies, an indefinite duration of therapy may be a better option. Another question that should be tested is whether lenalidomide, an IMiD with lower incidence of neurotoxicity, that showed a single agent activity in the MCL or the BTK

inhibitor ibrutinib might be effective agents for maintenance therapy after administration of aggressive front line regimens.

In summary, this study has demonstrated that an intensive induction regimen with diligent supportive care can achieve high response rates, and subsequent maintenance therapy may lead to long-term remissions in MCL. Some of the patients treated on the UM-MCL1 remain in complete remission after over 10 years follow-up, suggesting that a cure may have been achieved; this challenges the paradigm that MCL is incurable and provides a strong rationale for testing this regimen further. Having fine-tuned the induction phase, the next step would be to test different maintenance regimens to further improve the survival rates. If the PFS of the UM-MCL2 rituximab maintenance patients mirrors the thalidomide maintenance group after longer follow-up, we plan to initiate a subsequent trial combining rituximab and lenalidomide maintenance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by grants to ISL: NIH CA109335, the Dwoskin Family and Recio Foundations.

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Figure 1A

Figure 1B

Figure 1C

Figure 1D

Figure 1.

Kaplan-Meier survival curves showing progression-free survival (panel 1A), overall survival (panel 1B), and the stratification of progression-free survival and overall survival by mantle cell lymphoma international prognostic index (MIPI) risk groups (panels 1C and 1D respectively).

Table 1

Baseline characteristics

	N	%
Age		
Median (range)	56.6 years (39 – 73)	
< 50 years	7	19.4
50–59 years	15	41.7
60–69 years	10	27.8
70 years	4	11.1
Sex		
Female	10	27.8
Male	26	72.2
ECOG performance status		
0	23	63.9
1	11	30.6
2	2	5.6
Ann Arbor stage		
III	2	5.6
IVA	17	47.2
IVB	17	47.2
Generalized lymphadenopathy	24	66.7
Splenomegaly	14	38.9
Hepatomegaly	5	13.9
Bone marrow involvement	30	83.3
Gastrointestinal involvement	18	50.0
Pleural effusion	6	16.7
Variants of MCL		
Diffuse	32	88.9
Blastic	4	11.1
β_2-microglobulin		
Median (range)	3.09 mg/dl (1.5–14.7)	
< 3 mg/dl	17	47.2
3 mg/dl	19	52.8
Ki-67%		
Median (range)	44% (5 – 90%)	
< 10%	1	2.8
10–29%	10	27.8
> 30 %	15	41.7
Missing	10	27.8
MIPI risk score		
Low risk	19	52.8

	N	%
Intermediate risk	13	36.1
High risk	4	11.1

Abbreviations: ECOG: Eastern Cooperative Oncology Group; MCL: Mantle Cell Lymphoma; MIPI: Mantle cell lymphoma International Prognostic Index.

Table 2

Adverse events during the chemotherapy induction phase

	R-MACLO, 70 cycles		R-IVAM, 66 cycles	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Neutropenia	2 (3%)	38 (54%)	4 (6%)	37 (56%)
Anemia	19 (27%)	26 (37%)	10 (15%)	47 (71%)
Thrombocytopenia	13 (18%)	24 (34%)	3 (4%)	56 (85%)
Febrile neutropenia	0	16 (23%)	0	28 (42%)
Infection	6 (8%)	12 (17%)	9 (14%)	19 (29%)
Bacteremia	0	4 (6%)	0	16 (24%)
Hyperglycemia	27 (38%)	1 (1%)	22 (33%)	2 (3%)
Hypokalemia	29 (41%)	1 (1%)	27 (41%)	1 (1%)
Elevated Creatinine	10 (14%)	1 (1%)	6 (9%)	0
Nausea	22 (31%)	1 (1%)	24 (36%)	0
Vomiting	8 (11%)	1 (1%)	14 (21%)	0
Mucositis	24 (34%)	4 (6%)	12 (18%)	0
Diarrhea	9 (13%)	5 (7%)	9 (14%)	1 (1%)
Constipation	14 (20%)	0	12 (18%)	1 (1%)
Dyspnea	8 (11%)	1 (1%)	6 (9%)	1 (1%)
Edema	9 (13%)	0	6 (9%)	0
Pleural effusion	3 (4%)	1 (1%)	1 (1%)	1 (1%)
Headache	17 (24%)	0	7 (11%)	0
Rash	14 (20%)	0	15 (23%)	0
Elevated AST/ALT	14 (20%)	0	11 (17%)	1 (1%)
Fatigue	13 (18%)	0	11 (17%)	1 (1%)

Abbreviations: ALT: Alanine Transaminase; AST: Aspartate Transaminase; R-IVAM: Rituximab, Ifosfamide, Etoposide, Cytarabine, Mesna; R-MACLO: Rituximab, Methotrexate, Doxorubicin, Cyclophosphamide, Leucovorin, Vincristine.

Table 3

Comparison of frontline mantle cell lymphoma regimens

Trial / Regimen	N	ORR	EFS/PFS	OS
Romaguera (2005) ³ R-HyperCVAD/MA × 6–8 cycles	97	97%	64% (3 yr PFS)	82% (3 yr OS)
Geisler (2008) ⁷ R-MaxiCHOP × 3 + High dose Ara-C × 2 → ASCT	160	96%	73% (4 yr PFS)	81% (4 yr OS)
Delarue (2013) ⁸ CHOP × 2 + R-CHOP × 1 + R-DHAP × 3 → ASCT	60	82%	64% (5 yr EFS)	75% (5 yr OS)
Hermine (2012) ²² R-CHOP × 3 + R-DHAP × 3 → ASCT	497	97%	88 mo (median TTF)	NR (median OS)
Le Gouill (2014) ²³ R-DHAP × 4 → ASCT → R _M or WW	299	92%	74% (3 yr PFS)	83% (3 yr OS)
Current study R-MACLO-IVAM × 4 cycles → Maintenance	36	97%	51% (5 yr PFS)	85% (5 yr OS)

Abbreviations: Ara-C: Cytarabine; ASCT: Autologous Stem Cell Transplantation; EFS: Event-Free Survival; N: Number of patients; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; R-DHAP: Rituximab, Dexamethasone, Cytarabine; Cisplatin; R-HyperCVAD/MA: Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, Methotrexate, Cytarabine; R_M: Rituximab maintenance; R-MACLO-IVAM: Rituximab, Methotrexate, Doxorubicin, Cyclophosphamide, Leucovorin, Vincristine, Ifosfamide, Etoposide, Cytarabine, Mesna; WW: Watchful waiting.