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Treatment of IgM-associated immunoglobulin light chain amyloidosis with Rituximab-Bendamustine

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Systemic AL amyloidosis (AL) is characterised by deposition of misfolded immunoglobulin light chains within organs. AL with an IgM monoclonal protein (IgM-AL) accounts for 5-7% of AL and exhibits more prevalent lymph node, neuropathic and lung involvement, less prevalent cardiac involvement and lower amyloidogenic light chains.[1] A reduction in intact monoclonal protein and free light chains is prognostic.[1] A very good partial response (VGPR) is associated with better survival and organ responses but is challenging to achieve due to an unclear underlying diagnosis (usually lymphoplasmacytic lymphoma) and lack of treatment uniformity. In a large retrospective study, we reported the use of twenty-two front-line regimens.[1] Rituximab-based regimens are often used alongside bortezomib, alkylators or purine analogs; outcomes remain poor with few complete responses.[1-3] Excellent haematological responses were reported in 12 IgM-AL patients treated with autologous stem cell transplantation[4] – but given the older age of IgM-AL patients, this is often not an option. Treatment of relapsed/refractory patients is particularly challenging and recent experience with ibrutinib was disappointing.[5]

Bendamustine, which has features of an alkylator and purine analog, is used alongside rituximab in newly diagnosed and relapsed/refractory non-Hodgkin lymphoma[6] and in relapsed/refractory Waldenstrom's Macroglobulinaemia (WM) with overall haematological response rate (ORR) of 83.3%.[7] Bendamustine in relapsed/refractory AL (with a plasma cell dyscrasia) resulted in disappointing responses.[8] There have been no studies focusing on the use of rituximab-bendamustine (BR) in IgM-AL. We report efficacy of BR in untreated and relapsed/refractory IgM-AL.

Twenty-seven patients treated with BR between 2011-2017 were identified from the UK National Amyloidosis Centre database: twenty-two received BR first-line therapy and five as second-line.

Twenty-five had a serum IgM M-protein. Two had lymphoplasmacytic lymphoma on bone marrow examination but had a serum IgG M-protein (instead of IgM).

AL was confirmed on biopsy immunohistochemistry or proteomic analysis. All patients underwent serial biochemical tests for organ function, cardiac biomarkers, serum free light chains, serum and urine protein electrophoresis and immunofixation, echocardiography +/- cardiac MRI (unless contraindicated). Organ involvement was defined by international amyloidosis consensus criteria.[9] Haematological responses were assessed according to AL amyloidosis response criteria.[10] In patients with non-evaluable serum free light chains (dFLC<50mg/L), IgM M-protein was used for assessment.

Rituximab (375mg/m^2) was administered intravenously on Day 1 as per local protocols. Bendamustine (90mg/m^2) was administered intravenously over 30 minutes on Day 1 and 2. Four patients received additional corticosteroid therapy (three received weekly dexamethasone 20mg, one received once weekly dexamethasone 10mg). BR was repeated every 28 days.

Outcome variables were haematological and organ response, overall survival (OS) progression-free survival (PFS, progression defined as progression to next treatment or death), and time-to-next-treatment (TNT).

Table 1 shows baseline characteristics. Median age was 70 years (56-86 years). Cardiac, renal, liver, peripheral nerve, autonomic nerve and soft tissue involvement were found in 17 (63%), 17 (63%), 6 (22%), 6 (22%), 4 (15%), 2 (7%), respectively. Lymphadenopathy was radiologically identified in 13 (48%); 7 (26%) had biopsy-proven lymph node amyloid deposition. The Mayo 2004 cardiac stage was: Stage I 30%, Stage II 48% and stage III 22%. Median M-protein was 11.5g/l (1-30g/l); 19

(70.4%) had evaluable free light chains. Of the remaining patients, all had an IgM M-protein (>5g/l) enabling response assessment.[10]

Twenty-one patients had available bone marrow data (trephine +/- flow cytometry): three normal, one plasma cell infiltration, fourteen lymphoplasmacytic lymphoma and three NHL not specifically classified. Five patients were treated with BR for refractory disease, previous therapies included bortezomib-cyclophosphamide-dexamethasone in two and in one case each: rituximab-bortezomib-dexamethasone, rituximab-cyclophosphamide-vincristine-prednisolone and rituximab-cyclophosphamide-dexamethasone.

The median number of BR cycles was 5 (range 1-8). The median number of previous cycles in the second-line group was 6 (range 4-8). Three patients received two-monthly rituximab maintenance (375mg/m^2 intravenously) after first-line therapy with BR. All three remain on rituximab maintenance, with treatment duration thus far of 8, 10 and 11 months.

ORR on an intention-to-treat (ITT) and evaluable basis was 59% and 76%, respectively. Haematological responses (ITT) were: complete response (CR) 11%, VGPR 37%, partial response (PR) 11% and no-response (NR) 41% (including 22% deaths). In the first-line group, haematological responses were: CR 14%, VGPR 32%, PR 14% and NR 40% (including 18% deaths). The evaluable responses were: CR 17%, VGPR 39%, PR 17% and NR 27%. Of three patients treated with two-monthly rituximab maintenance, one remains in VGPR, one in CR (having been in VGPR at time of completing BR) and one in PR (non-responder at time of completing BR). In five treated for refractory AL, three achieved a VGPR and two were non-responders (including one death). 3/17

patients with cardiac involvement achieved NT-proBNP responses and 3/17 patients achieved renal responses by consensus criteria.[10]

Median follow-up was 18 months (3-55 months). Median OS was not reached (Figure 1A). Median OS was not reached in patients who achieved VGPR/better, compared to 9 months in patients who did not (Figure 1B). Median PFS was 34 months. Five patients (18.5%) died within six months of diagnosis (three Mayo Stage II, two Stage III). On six month landmark analysis, median PFS was not reached. Of patients in the 6 month landmark analysis who achieved VGPR/better, median OS and PFS were not reached (compared to 34 and 11 months, respectively, in patients who did not). Three patients progressed to next treatment (their response to BR was VGPR, PR and non-response). Median TNT was not reached, with 88% and 79% of evaluable patients (n=17) not progressing to next treatment at 1 and 3 years, respectively (Figure 1A).

Grade 3-4 toxicity included: diarrhoea 1 (3.7%), hypotension 2 (7.4%), non-neutropenic infection (11.1%), neutropenia 2 (7.4%), febrile neutropenia 2 (7.4%) (resulting in bendamustine dose reduction to 60mg/m^2), rash 1 (3.7%), fluid overload 2 (7.4%) and GI bleeding 1 (3.7%). The most frequent Grade 1-2 toxicities were constipation (26%) and fatigue (30%).

The data from this small retrospective study demonstrates excellent haematological responses. Impressively, 48% achieved VGPR/better (ITT). Sixty percent of patients treated with BR second-line achieved a VGPR. Furthermore, rituximab maintenance upgraded responses in the few patients that received this therapy.

Treatment in IgM-AL is not uniform, with poor responses to alkylators (responses 27-38%[2,11,12]) or purine-analogue/anthracycline-containing therapy [1,2]. Outcomes with bortezomib-based therapy are mixed: VGPR/better 27% and 42% in two studies.[1,13]. A rituximab-bortezomib combination improved responses, with ORR of 78%.[3] The high prevalence of disease-related neuropathy in IgM-AL provokes reticence in using bortezomib. Furthermore, bortezomib is not funded in the UK for lymphoproliferative disorders. The few patients eligible for ASCT appear to have good outcomes (ORR 89% and 67% organ responses) but transplant-related mortality was 8%.[4] In a large European study, only 1.8% of patients were treated with ASCT.[1] Disappointingly, the efficacy of ibrutinib in WM (ORR of 91%) [14] was not replicated in AL.[5]

In conclusion, this study suggests that first-line BR leads to high response rates in IgM-AL. Bendamustine is not neurotoxic, dosing is not affected by renal impairment and there is no known cardiac toxicity, rendering BR a widely applicable therapy in IgM-AL. Response appears durable and maintenance rituximab may upgrade depth of response. The limitation of this study is one shared with almost all literature in IgM-AL given its rarity: it is small and retrospective. Larger collaborative studies are needed to confirm these results and combination with novel proteasome inhibitors should be explored to further improve outcomes.

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Authorship contributions

RM and AW designed the manuscript, collected and analysed data, and wrote the paper. The remaining authors managed the patients and provided critical input prior to submission.

Disclosure of conflict of interest

None of the authors have any relevant conflicts of interest to disclose.

Institutional review board approval

The Alchemy study is performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 2000. Informed written consent is obtained from the patients prior to registration into the study. The right of a patient to refuse participation without giving reasons is respected. Patients remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. Study granted approval by the appropriate NHS Research Ethics Committee.

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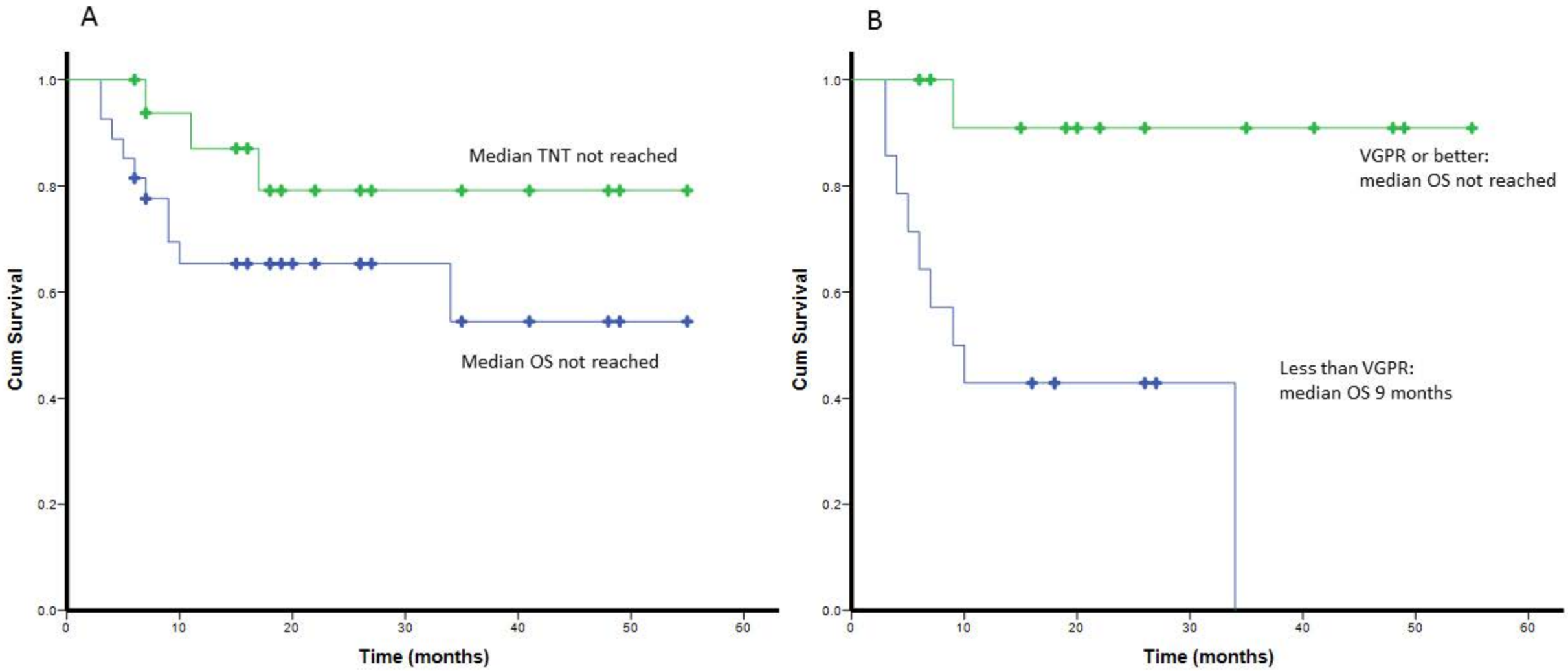
Table 1. Baseline characteristics.

n=27	Median (range) / n(%)
Median age (years)	70 (range 56-86)
Male:Female	16 (59%):11 (41%)
NYHA class 1 2 3 4	 12 (44%) 14 (52%) 1 (4%) 0
ECOG 0 1 2 3 4	 7 (26%) 15 (56%) 5 (18%) 0 0
Cardiac involvement	17 (63%)
Median NT-proBNP (ng/l)	978 (range 42-5708)
Median cardiac troponin T (ng/l)	31.5 (range 3-122)
Mayo Stage I II IIIA (NT-proBNP ≤8500ng/l) IIIB (NT-proBNP>8500ng/l)	 8 (30%) 13 (48%) 6 (22%) 0
Median systolic blood pressure (mmHg)	119 (range 100-164)
Median left ventricular wall thickness (mm)	11 (range 8.5-18)
Median LV ejection fraction (%)	60 (range 36-72)
Renal involvement	17 (63%)
Median serum creatinine (umol/l)	98 (range 46-493)
Median GFR (ml/min)	68 (range 10-100)
Median proteinuria (g/24h)	0.8 (range 0.1-34.6)
Liver involvement	6 (22%)
Median serum bilirubin (umol/l)	6 (range 2-50)
Median ALP (units/l)	105 (range 25-1879)
Soft tissue involvement	2 (7%)
Peripheral nerve involvement	6 (22%)
Autonomic nerve involvement	4 (15%)
Lymph node involvement	13 (48%)
GI involvement	0
Median number of involved organs	1 (range 1-4)
Involved light chains: Kappa Lambda No monoclonal light chain excess	 7 (26%) 12 (44%) 8 (30%)
Median dFLC (mg/l)	59.8 (range 2.2 – 856.4)
IgM kappa M-protein IgM lambda M-protein	11 (44%) 14 (56%)
Median serum monoclonal protein (g/l)	11.5 (range 1-30)

Figure 1. Overall survival (OS) and time-to-next-treatment (TNT). A) This shows the overall survival (OS) on an ITT basis (n=27) and time-to-next-treatment (TNT) on an evaluable basis (n=17). Median OS and median TNT were not reached. OS at 1 year and 3 years was 65% and 56%. **At 1 and 3 years, 88% and 79% of evaluable patients (n=17) had not progressed to further treatment.** B) Median OS was not reached in those patients who achieved a very good partial response (VGPR) or better with 92% alive at 2 years; median OS was 9 months in patients who did not achieve a VGPR.


A
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Time (months)
Median TNT not reached
Median OS not reached
B
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Time (months)
VGPR or better:
median OS not reached
Less than VGPR:
median OS 9 months

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