



## **Evidence Review:**

# **Haematopoietic Stem Cell Transplantation (HSCT) for Lymphoplastic Lymphoma (Adults)**

## NHS England

### Evidence Review:

# Haematopoietic Stem Cell Transplantation (HSCT) for Lymphopasmacytic Lymphoma (Adults)

First published: January 2016

Updated: N/A

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## 1. Introduction

Lymphoplasmacytic Lymphoma is a rare form of slow growing non-Hodgkin Lymphoma (NHL). It occurs when a type of white blood cell, called plasma cells, become abnormal and grow out of control. The abnormal plasma cells build up in the bone marrow and sometimes in the lymph nodes, spleen and other organs. They make large amounts of a protein called IgM, which can make the blood thicker than normal.

Haematopoietic stem cell transplantation (HSCT), also known as blood and marrow transplantation (BMT) is used to treat wide spectrum of haematological, and increasingly, non-haematological disorders. It is broadly divided into two main groups: autologous and allogeneic transplantation.

Allogeneic haematopoietic stem cell transplantation (HSCT) is used to treat carefully selected patients with a range of malignant and non-malignant blood-related disorders and other specific disorders of the immune system. It involves replacing the bone marrow stem cells of a patient following high-dose therapy, with stem cells from a tissue-type matched or mismatched donor.

Autologous transplantation uses the patient's own stem cells, which are harvested prior to high-dose therapy. It enables the patient to be treated with doses of chemotherapy which are higher than would be possible without subsequent replacement of the harvested cells, because the therapy destroys the patient's remaining stem cell tissue.

## 2. Summary of results

This review aimed to address the following research questions:

1. Is there sufficient quality evidence of clinical effectiveness to support new S and CO recommendations for haematopoietic stem cell transplant for Lymphoplasmacytic Lymphoma?
2. Is there any evidence to indicate the comparative effectiveness of HSCT compared to other management strategies for Lymphoplasmacytic Lymphoma?
3. Is there evidence to indicate the cost effectiveness compared to other management strategies?

### Part 1: Quality of evidence

Given the rarity of lymphoplasmacytic lymphoma (LL), also known as Waldenstrom's macroglobulinaemia (WM), and the heterogeneous pre-treatment that patients had received prior to haematopoietic stem cell transplantation (HSCT), results from the literature search have been scarce and inconclusive. Studies were mostly retrospective, and often had small patient sample sizes (Caravitas et al., 2009; Dreger et al., 2007). There is a potential risk of selection bias in the studies given that more immunocompetent and younger patients would be offered transplant. Moreover, there were no randomised controlled trials or systematic reviews conducted to assess HSCT as a treatment for LL. Any policy recommendation will therefore be delivered with these caveats attached.

### Autologous vs. Allogeneic

A study with 36 patients favoured autologous HSCT (autoSCT) over allogeneic HSCT (alloSCT) because of the higher overall survival (OS) rates (70% vs. 46% at 3 years) and progression free survival (PFS) rates (65% vs. 31% at 3 years) (Anagnostopoulos et al., 2006).

In 2010, Kyriakou et al. published two retrospective studies with large patient samples using data reported to the European Blood and Bone Marrow Transplantation Group (EBMT) Registry between January 1991 and 2005. The two papers together were used to compare the clinical outcomes of WM patients who had undergone autologous HSCT (158 patients) and allogeneic HSCT (86 patients). One paper (Kyriakou et al., 2010a) showed that autologous stem cell transplant (autoSCT) combined with high dose therapy had low levels of toxicity and an acceptable level of non-relapse mortality (NRM) of 3.8% at 1 year. Overall survival (OS) rates were 68.5% at 5 years, while progression free survival (PFS) was 39.7%. Patients who received autoSCT at VGPR1/PR1 had better outcomes, with PFS at 73% and OS at 77% at 5 years. However, patients who were chemorefractory or had received at least 3 lines of treatment had a significantly inferior PFS and OS, and other prognostic risk factors identified include age of over 50 years and male sex. These findings suggest that autoSCT is most effective for younger patients who receive transplantation at first response. The other paper (Kyriakou et al., 2010b)

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investigated the effectiveness of allogeneic SCT in the treatment of WM. Overall, NRM at 5 years was at 27%, and the 5-year OS and PFS were 64% and 52%, respectively, but it was not clear how patients who were CR/PR1, CR/PR>1, chemorefractory or primary resistant responded. The study concluded that donations taken from HLA-identical siblings or a matched unrelated donor (MUD) did not result in any statistical difference in NRM. Read together, the two papers support the view that HSCT is effective in triggering a response in WM patients. However, patient selection is of paramount importance. In general, young patients with high-risk WM, as defined by the International Prognostic Scoring System for Waldenström's macroglobulinemia (IPSSWM) appear to have better responses and OS rates. For autoSCT, VGPR1/PR1 patients performed well whereas alloSCT was recommended for chemorefractory, chemoresistant patients and those who have failed autoSCT. In corroboration of this data, Usmani et al. (2011) presented evidence from a 158 patient study on autoSCT to show that post-transplantation, naive patients at 5 years had better PFS than heavily pre-treated patients (76% vs.68%) and OS (49% vs. 41%), though neither of these figures are statistically significant.

### **Graft-versus-host disease effect in the context of safety**

Anagnostopoulos et al. (2006) concluded with a patient sample size of 36 patients that alloSCT also had higher non-relapse mortality rates, at 40% after 3 years, as opposed to 11% for autoSCT. This finding is supported by Gilleece et al. (2008), who found autoSCT to be a safe treatment, with no transplant-related mortalities (TRM) at 1 year. Dreger et al. (2007) also reported that autoSCT was a safe procedure with 100% OS at a median follow up of 69 months, although the reliability of the data was marred by the small (n=12) patient sample size. The much larger study by Kyriakou et al. (2010b) has similar findings, reporting that alloSCT was more toxic than autoSCT; 5-year NRM was 27% for alloSCT, compared to 5.8% for autoSCT. However, the higher PFS seen in alloSCT patients was attributed to a chronic graft-versus-host disease (GVHD) effect. Curiously, the OS in the alloSCT sample plateaued at a steady 64% at 5 years after transplantation, whereas the same figure in the autoSCT sample dropped from 68.5% to approximately 57% from year 5 to year 8.

### **Allogeneic transplantation - HLA-identical sibling vs. matched unrelated donor (MUD)**

Gilleece et al. (2008) had only 1 MUD patient; the endpoint outcomes of HLA-identical vs. MUD donors could therefore not be evaluated. Meanwhile, Kyriakou et al. (2010b) did not find any difference in the NRM of HLA-identical and MUD donors. Other studies reported the number of patients who received HLA-identical sibling or matched unrelated donor (MUD) allografts, but did not explicitly state patient observations or endpoint outcomes. As such, the paucity of evidence makes it impossible to draw a conclusion on the difference in effectiveness between the two types of allografts.

Overall, the data suggests that autoSCT is a safer therapy option compared to alloSCT, and seems to show higher efficacy to patients who are naive or in PR1. AlloSCT, on the other hand, is more toxic but can result in good PFS. However, the fact that most patients undergoing alloSCT were usually more heavily pre-treated or had greater disease severity at the time of transplantation precludes a definitive conclusion.

## **Part 2: Comparative effectiveness versus other management strategies**

Usmani et al. (2011) reported that patients who underwent autoSCT showed better response compared to those who received other types of therapy (21% in CR vs.17%; 67% in PR vs.18%), resulting in higher PFS at 5 years, 69% vs. 41%. OS was similar at 5 years, but OS plateaued and remained high at 78% up until year 12, whereas patients who did not receive a transplant only had an OS of 40% at 12 years.

## **Part 3: Cost effectiveness**

There were no studies specifically addressing the clinical and cost effectiveness of haematopoietic stem cell transplantation for the treatment of Lymphoplasmacytic Lymphoma compared to usual care options such as treatment with nucleoside analogues, alkylating agents and rituximab.

### **3. Research questions**

1. Is there sufficient quality evidence of clinical effectiveness to support new S (standard of care) and CO (clinical option, can be considered after assessment of risks and benefits) recommendations for haematopoietic stem cell transplant for Lymphoplasmacytic Lymphoma?
2. Is there any evidence to indicate the comparative effectiveness of HSCT compared to other management strategies for Lymphoplasmacytic Lymphoma?
3. Is there evidence to indicate the cost effectiveness compared to other management strategies?

### **4. Methodology**

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

### **5. Results**

A detailed breakdown of the evidence is included in the Appendix.

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Appendix One

Grade		Study design and intervention			Population		Outcomes				Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Disease severity	Sub group	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
3	Cohort	12	Four patients proceeded directly to Dexamethasone-BEAM mobilisation, whereas the remainder received 3-6 cycles of CHOP (4), R-CHOP (2), chlorambucil (1), or fludarabine (1) before mobilisation. Myeloablative therapy with total body irradiation (TBI)/high-dose cyclophosphamide and stem cell reinfusion was given before autologous stem cell transplantation (ASCT). In the first 5 patients, grafts were vigorously B cell-depleted by immunomagnetic CD34+ and/or negative B cell selection.	Adequate performance status (Karnofsky $\geq 80\%$ ). Naïve to cytotoxic treatment	Median time to treatment was 82 months. 5 out of 8 patients who received pre-treated patients who underwent chemotherapy achieved partial remission; the rest had no response	-	Not explicitly stated; inferred to be overall survival (OS); progression-free survival (PFS); and non-relapse mortality (NRM)	Median PFS is 69 months. OS at (median) 69 months is 100%.	-	-	Dreger, Peter; Schmitz, Norbert. Autologous stem cell transplantation as part of first-line treatment of Waldenström's macroglobulinemia. Biol. Blood Marrow Transplant.. 2007.	-	-	This was a small study including 12 patients. The paper was a letter to the editor and therefore very brief. The intervention methodology was not clearly stated; for e.g. the source of the stem cells (peripheral blood vs. bone marrow) was not stated. Post-ASCT treatment was also not reported. Note that the age of the selected patients was young, which is an important caveat to include when assessing the author's positive conclusion on ASCT's efficacy in treating WM. Given the lack of clarity, it is most likely that a biased view was presented.
3	Case series	5	Rituximab and CHOP (a chemotherapy conditioning regimen) followed by cyclophosphamide mobilisation. Then autologous HSCT and melphalan conditioning.	-	Male patients suffering from WM	-	-	OS, DSF, NRM	-	-	Caravita, T.; Siniscalchi, A.; Tendas, A.; Cupelli, L.; Dentamaro, T.; Natale, G.; Spagnoli, A.; de Fabritius, P.. High-dose therapy with autologous PBSC transplantation in the front-line treatment of Waldenström's macroglobulinemia. Bone Marrow Transplant.. 2009.	-	-	This study could not be included in the review given the limited information on the study methodology and outcomes. It was printed as a letter to the editor and forms part of the BSBMT series.

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2++	Cohort	86	SG1 received high dose cyclophosphamide and total body irradiation, or cyclophosphamide and other chemotherapy protocols. 51% received PBSC, 49% used bone marrow stem cells. SG2 received fludarabine with either an alkylating agent or total body irradiation. 96% used PBSC, 4% used bone marrow stem cells. After conditioning, all patients underwent allogeneic SCT.	47 patients had received three or more previous lines of therapy. 8 patients had experienced failure on a prior autologous stem-cell transplantation. 59 patients had chemotherapy-sensitive disease at the time of allogeneic SCT.	Two subgroups: Myeloablative subgroup (SG1), (n=37) and reduced-intensity (SG2), (n=49) conditioning	-	OS, DFS, NRM, toxic mortality rate (TRM), graft-versus-host disease (GVHD)	Overall: NRM at 3 years was 27%. RR = 75.6%, relapse rates at 3 years = 19%. At 5 years, PFS = 52% and OS = 64% SG1: NRM at 3 years was 33%. RR = 75.6%, relapse rates at 3 years = 11%. At 5 years, PFS = 56% and OS = 62% SG2: NRM at 3 years was 23% RR = 75.6% relapse rates at 3 years = 25%. At 5 years, PFS = 49% and OS = 64%	-	-	Kyriakou, Charalampia; Canals, Carmen; Cornelissen, Jan J.; Socié, Gerard; Willemze, Roel; Ifrah, Norbert; Greinix, Hildegard T.; Blaise, Didier; Deconinck, Eric; Ferrant, Augustin; Schattenberg, Anton; Harousseau, Jean-Luc; Sureda, Anna; Schmitz, Norbert. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J. Clin. Oncol.. 2010.	-	-	Given the rarity of WM, this study had a large patient sample. Results support alloSCT as a viable treatment option, and there is evidence to support that it is effective at triggering a response. Additionally, the PFS of this treatment option is higher than autologous SCT and relapse rates are lower. However, NRM was this procedure is much higher than for autologous transplants. This set of results indicates that HSCT, and in particular alloSCT, will be most effective for a patient subpopulation that is young, not heavily pre-treated and suffer from high-risk WM, as defined by IPSSWM.
2+	Cohort	27 (but 29 transplantations), split into 2 subgroups (SGs)	Autologous (SG1) and allogeneic (SG2) transplantation. Median interval between diagnosis and transplant was 36 months (range, 7 to 252). SG1 - source of cells came from unmanipulated periphery blood progenitor cells (UPBC), except in one patient who received both UPBC and bone marrow progenitor cells. Patients received either mobilisation by granulocyte colony-stimulating factor (G-CSF) or chemotherapy plus G-CSF).	SG1 - 14 patients (78%) were chemosensitive, and 4 patients (22%) were chemoresistant. 12 patients (66% of subgroup 1) had undergone 3 or more chemotherapy regimens. SG2 - 6 patients (60%) were chemosensitive, and 4 patients (40%) were chemoresistant. 6 patients (60% of subgroup 2) had undergone 3 or more chemotherapy regimens. 19 patients (66%) had received 3 or more treatment regimens. 21 patients (72%) had chemosensitive disease, 8 patients (28%) had refractory disease.	SG1 -19 patients for autologous transplant. SG2 - 10 for allogeneic transplant. Two patients underwent two transplantations each, one having two autologous transplantations, the other having first an autologous followed by an allogeneic transplantation.	-	OS, DFS, NRM, toxic mortality rate (TRM)	SG1 - At median follow-up of 18 months, OS = 66%. At 10-34 months, DFS = 44%. Progression occurred in 9 patients (50%) at a median of 10 months. 6 patients (33%) died at 3 to 17 months, 4 from disease progression and 2 from toxicity. TMR is 6% at 17 months. SG2 - At median follow-up of 20.5 months. OS and DFS are both at 60%. 5 patients (50%) achieved complete response (CR). Progression occurred in 3 patients (33%). TRM was 40% at 76 months. 1 patient died from thrombotic microangiopathy and the other 3 from toxicity.	-	-	Tournilhac, O.; Leblond, V.; Tabrizi, R.; Gressin, R.; Senecal, D.; Milpied, N.; Cazin, B.; Divine, M.; Dreyfus, B.; Cahn, J. Y.; Pignon, B.; Desablens, B.; Perrier, J. F.; Bay, J. O.; Travade, P.. Transplantation in Waldenström's macroglobulinemia--the French experience. Semin. Oncol.. 2003.	SG2 - Acute graft-versus-host disease occurred in 7 patients	The study compared the prognosis of autologous vs. allogeneic stem cell transplantation. One limitation is the small patient sample size (36 in total), and the imbalance between the number of patients in each subgroup. In the allogeneic transplant subgroup, one patient had already undergone autologous transplant beforehand, making the results for this individual difficult to interpret.	



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3	Cohort	25	Allogeneic stem cell transplantation after myeloablative (n=12) or reduced-intensity (n=13) conditioning. In SG1, stem cell source was bone marrow. In SG2, stem cell source was peripheral blood in 11 patients, bone marrow in one, and cord blood in one.	Previously received a median of 3 lines of therapy (range, 1-6). 11 patients (44%) had refractory disease at time of transplantation (4 stable and 7 progressive disease) and 14 patients (56%) had chemosensitive disease (13 partial response and one very good partial response). One patient had WM transformation into large B-cell lymphoma.	Two subgroups: Myeloablative subgroup (SG1), (n=12) and reduced-intensity (SG2), (n=13) conditioning. 11 males and 4 females.	-	Post-transplant response rate (RR), OS, PFS. Transplant related mortality (TRM) and progression. Acute or chronic graft-versus-host disease (GVHD)	The overall response rate was 92%, with a complete remission in 50% of evaluable patients at the last follow up. At 5 years, OS = 67% (95% CI: 46-81) and PFS = 58% (95% CI: 38-75). Risk of progression was 25% (95% CI: 10-36%). Of the 12 patients entered CR, 1 had a relapse. Of the 12 patients who did not enter CR, 5 had a relapse.	RR = 92%	-	Garnier, Alice; Robin, Marie; Larosa, Fabrice; Golmard, Jean-Louis; Le Gouill, Steven; Coiteux, Valérie; Tabrizi, Reza; Bulabois, Claude-Eric; Cacheux, Victoria; Kuentz, Mathieu; Dreyfus, Brigitte; Dreger, Peter; Rio, Bernard; Moles-Moreau, Marie-Pierre; Bilger, Karin; Bay, Jacques-Olivier; Leblond, Véronique; Blaise, Didier; Tournilhac, Olivier; Dhédin, Nathalie. Allogeneic hematopoietic stem cell transplantation allows long-term complete remission and curability in high-risk Waldenström's macroglobulinemia. Results of a retrospective analysis of the Société Française de Greffe de Moelle et de Thérapie Cellulaire. Haematologica. 2010.	-	-	This study shows that allogeneic SCT transplantation is effective in inducing a response rate and even complete response in half of the patients. The relatively small patient sample size limited the original comparison between reduced-intensity and myeloablative conditioning on patient remission, relapse and survival.
2++	Cohort	158	Autologous haematopoietic stem cell transplant, with 23% receiving granulocyte colony-stimulating factor (G-CSF) alone as a mobilisation therapy, 77% receiving chemotherapy +G-CSF, 45 patients (28%) had total body irradiation (TBI) as a conditioning regimen, while the remaining 113 (72%) received chemotherapy.	37% patients presented with intermediate-risk disease, and 54% with high-risk disease (defined by the WM International Prognostic Scoring System (IPSS). 32% of the patients experienced treatment failure with at least three lines of therapy, 93% had sensitive disease at the time of autologous stem cell transplantation (ASCT).	-	-	PFS, NRM, OS	Out of the 155 patients (out of 158 total) for whom ASCT could be evaluated, at median follow up (4.2 years, range 0.5 to 14.8 years), 68% are alive and 32% have died, 26% of disease progression. Cumulative incidence of NRM is 3.8% at 1 and 2 years post-ASCT, and 4.6% at 3 years post-ASCT, and 5.6% at 5 years post-ASCT. The estimated OS rates at 3 and 5 years were 77.6% (95% CI, 71% to 84%) and 68.5% (95% CI, 60% to 77%), respectively. 49% were alive and remained progression free, with estimated PFS rates of 61.7% (95% CI, 54% to 70%) and 39.7% (95% CI, 31% to 50%) at 3 and 5 years, respectively. 45% have relapsed or progressed, with a median time from transplantation of 1.3 years (range, 0.1 to 5.1 years) and estimated relapse rates of 33.7% (95% CI, 27% to 42%) and 53.8% (95% CI, 44% to 62%) at 3 and 5 years, respectively. 6.3% developed a secondary malignancy after ASCT.	-	-	Kyriakou, Charalampia; Canals, Carmen; Sibon, David; Cahn, Jean Yves; Kazmi, Majid; Arcese, William; Kolbe, Karin; Gorin, Norbert Claude; Thomson, Kristy; Milpied, Noel; Niederwieser, Dietger; Indrák, Karel; Corradini, Paolo; Sureda, Anna; Schmitz, Norbert. High-dose therapy and autologous stem-cell transplantation in Waldenström macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J. Clin. Oncol.. 2010.	-	-	This study focused on autologous SCT (ASCT), and compared OS, PFS and NRM across patients with different pre-treatment histories. This study has a good sample size (n=158), very clear reporting of patient disease severity at the time of ASCT, and a good reporting of primary outcomes that supports that ASCT produces a high RR, and low NRM at 5 years. However, prognosis for heavily pre-treated or chemorefractory patients is somewhat poorer, with a higher incidence of relapse.

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2+	Systematic	18	SG1 - high dose chemotherapy and transplantation using peripheral blood stem cells (PBSC). SG2 - allogeneic transplantation were conditioned with TBI or chemotherapy, and received PBSC from HLA-matched sibling or unrelated donors.	Overall: Complete remission (11%), partial remission (67%), primary refractory (17%), relapse (5%). SG1: complete remission (2 patients, 22%), partial remission (5, 56%), primary refractory (1 patient, 11%) or relapse (1 patient, 11%). SG2: partial remission (7 patients, 78%) or primary refractory (2 patients, 22%).	SG1 - 9 patients undergoing autologous SCT. SG2 - 9 patients undergoing allogeneic SCT.	-	PFS, TRM, OS	Overall: TRM = 44% at 1 year, DFS = 44% at 4 years, OS = 56% at 5 years SG1: at 12-month follow up, TRM = 0%. At median 44-month follow up, DFS = 43%, OS = 73% SG2: at 12-month follow up, TRM = 44%. At median 32-month follow up, DFS = 44%, OS = 56%	-	-	Gillece, Maria H.; Pearce, Rachel; Linch, David C.; Wilson, Marie; Towilson, Keiren; Mackinnon, Stephen; Potter, Michael; Kazmi, Majid; Gribben, John G.; Marks, David L. The outcome of haemopoietic stem cell transplantation in the treatment of lymphoplasmacytic lymphoma in the UK: a British Society Bone Marrow Transplantation study. Hematology. 2008.	-	-	The study has symmetrical patient numbers in the subgroups, and clearly reports the chemotherapy regimen received by all patients prior to transplantation. Patients at the time of transplant in both subgroups were relatively young and within a comparable age range, which is important for overall survival and transplant related mortality figures. The biggest limitation of this study will be the small sample size, making results inconclusive on their own.
2++	Cohort	158 WM patients screened; 36 patients with comprehensive data considered (out of a total of 57 patients who had received SCT)	Either autologous or allogeneic stem cell transplant (SCT). Median follow-up of 65 months (range, 24-103 months). 7 of the 10 patients in the autologous SCT group received mobilized peripheral blood stem cells (4 mobilized with chemotherapy plus growth factors; 3 with growth factors alone), and the other 3 received bone marrow as the stem cell source. Among the 26 patients in the allogeneic SCT group, 13 received a bone marrow graft, 12 received a peripheral blood stem cell graft, and 1 received both	A total of 78% of the patients had 2 or more previous chemotherapy regimens, and 52% had disease resistant to salvage chemotherapy. At the time of transplantation, 52% were resistant to salvage chemotherapy, and 33% were in at least PR.	36 patients with WM who received autologous (n = 10) or allogeneic (n = 26) SCT.	In the allogeneic SCT group, 58% of the patients received myeloablative conditioning regimens containing total body irradiation (TBI), and of the allograft recipients, 19% received nonmyeloablative/reduce-intensity conditioning.	Nonrelapse mortality (NRM), progression-free survival (PFS), overall survival (OS). Median time from initial treatment to SCT was 29 months (range, 2 - 198 months).	Nine patients (25%) achieved complete remission (CR) at 100 days post transplantation, 12 (33%) were in PR, 4 (11%) were in less than PR, 1 (3%) had progressive disease, and 10 (28%) were not evaluable/had died at 100 days. Primary disease accounted for 29% of the deaths in the allogeneic SCT group and 25% of the deaths in the autologous SCT group. NRM was 40% (95% CI, 23%-59%) for the allogeneic SCT group and 11% (95% CI, 0-36%) for the autologous SCT group at both 1 year and 3 years. PFS was 53% (95% CI, 36%-69%) at 1 year, with 44% (95% CI, 26%-63%) for the allogeneic group and 78% (95% CI, 47%-97%) for the autologous group, and 40% (95% CI, 14%-44%) at 3 years, with 31% (95% CI, 14%-50%) for the allogeneic group and 65% (95% CI, 32%-91%) for the autologous group. OS was 64% (95% CI, 48%-79%) at 1 year, with 58% (95% CI, 39%-76%) for the allogeneic group and 80% (95% CI, 51%-98%) for the autologous group, and 52% (95% CI, 36%-68%) at 3 years, with 46% (95% CI, 27%-65%) for the allogeneic group and 70% (95% CI, 40%-93%) for the autologous group.	-	-	Anagnostopoulos, Athanasios; Hari, Parameswaran N.; Pérez, Waleska S.; Ballen, Karen; Bashey, Asad; Bredeson, Christopher N.; Freytes, César O.; Gale, Robert Peter; Gertz, Morie A.; Gibson, John; Goldschmidt, Hartmut; Lazarus, Hillard M.; McCarthy, Philip L.; Reece, Donna E.; Vesole, David H.; Giralt, Sergio A.. Autologous or allogeneic stem cell transplantation in patients with Waldenstrom's macroglobulinemia. Biol. Blood Marrow Transplant.. 2006.	-	-	Allogeneic and autologous stem cell transplants were shown to have good primary outcomes, defined to be OS, DFS and NRM. Authors concluded that autologous SCT is a safer option than allogeneic SCT, which had a high NRM after 1 year, but were cautious in their recommendation of SCT as a treatment option, due to advanced age and high relapse rates. The majority of patients were heavily pre-treated, which made objective analysis of SCT's therapeutic efficacy more difficult to ascertain.

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3	Other	-	-	-	-	-	-	-	-	-	Gertz, M. A.; Reeder, C. B.; Kyle, R. A.; Ansell, S. M.. Stem cell transplant for Waldenström macroglobulinemia: an underutilized technique. Bone Marrow Transplant.. 2012.	-	-	This was a review paper similar to Bachanova et al., 2012, and summarises the patient outcomes for a selection of autologous vs. allogeneic SCTs for the treatment of WM.
3	Other	-	-	-	-	-	-	ASCT results in DFS of 45-65% at 5 years.	-	-	Bachanova, V.; Burns, L. J.. Hematopoietic cell transplantation for Waldenström macroglobulinemia. Bone Marrow Transplant.. 2012.	-	-	This was a review paper similar to Gertz et al., 2012, and summarises the patient outcomes for a selection of autologous vs. allogeneic SCTs for the treatment of WM.
3	Other	158 patients admitted for WM, 96 received therapy, 42 received Autologous stem cell transplantation (ASCT)	42 of 158 (27%) patients received autologous SCT (28 were previously untreated, 14 had received prior therapy)	95 of 158 (60%) patients had received no therapy prior to study, but 57 (36%) subsequently received therapy. 63 of 158 (40%) patients had been treated prior to study, and 39 continued to receive treatment (25%)	-	Patients who received "contemporary therapies". Extrapolated from introduction to assume a combination of any of the following: rituximab, chlorambucil, melphalan, cyclophosphamide, fludarabine, cladribine	Event free survival (EFS), OS, NRM	The median survival time for all patients requiring therapy was 9 years. The median EFS for patients receiving autologous SCT within 1 year following start of therapy at the institute was superior compared with patient not receiving a transplant, though this trend was not statistically significant (P = .06) (Figure 1D). The CR/nCR rates were 19%, 21%, and 17% for all WM patients, transplanted, and non-transplant patients, respectively. The PR rates were 39%, 67%, and 18% for the three respective groups.	-	-	Usmani, Saad; Sexton, Rachel; Crowley, John; Barlogie, Bart. Autologous stem cell transplantation as a care option in Waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2011.	-	-	This brief paper did not include segmented data on the pre-treatment and disease severity of the patient population that underwent transplantation. Primary end point outcomes suggest that the transplanted patients had a slightly higher CR than those who did not, as well as a better PR rate.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
Updated search terms - Population	Lymphoplasmacytic Lymphoma [MeSH Terms]
Updated search terms - Intervention	Haematopoietic stem cell OR HSCT OR Transplant OR Transplantation OR Transplants OR Transplantations OR Autograft OR Haematopoietic OR Haemopoietic OR Hemopoietic
Updated search terms - Comparator	Usual care Other effective management strategies
Updated search terms - Outcome	Overall survival Progression-free survival Cost-effectiveness Safety and complications Quality of life

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<b>Inclusion criteria</b>	<b>General inclusion criteria</b>
	<p>In order of decreasing priority, the following are included:</p> <ol style="list-style-type: none"> <li>1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available)</li> <li>2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available)              &gt;&gt;&gt;&gt; If studies included reach 30, inclusion stops here</li> <li>3. All relevant case control and cohort studies, that qualify after exclusion criteria              &gt;&gt;&gt;&gt; If studies included reach 30, inclusion stops here</li> <li>4. All relevant non analytical studies (case series/ reports etc) that qualify after exclusion criteria              &gt;&gt;&gt;&gt; If studies included reach 30, inclusion stops here</li> </ol>
<b>Exclusion criteria</b>	<b>Specific inclusion criteria</b>
	<p>Systematic review, meta-analysis, primary clinical study (any type)              Economic study (any type)              English only</p> <p>Include clinical references: BSMBT Indications for BMT, October 2013</p>
<b>Exclusion criteria</b>	<b>General exclusion criteria</b>
	<p>Studies with the following characteristics will be excluded:</p> <ol style="list-style-type: none"> <li>1. Do not answer a PICO research question</li> <li>2. Comparator differs from the PICO</li> <li>3. &lt; 50 subjects (except where there are fewer than 10 studies overall)</li> <li>4. No relevant outcomes</li> <li>5. Incorrect study type</li> <li>6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site</li> </ol>
<b>Exclusion criteria</b>	<b>Specific exclusion criteria</b>
	<p>None</p>

Haematopoietic Stem Cell Transplantation (HSCT) for Lymphopasmacytic Lymphoma (Adults)