DR. FAYE SHARPLEY (Orcid ID : 0000-0002-5908-0645)

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Autologous stem cell transplantation versus bortezomib for the first line treatment of systemic light chain amyloidosis in the UK

Faye A Sharpley,[1] Richa Manwani, [1] Aviva Petrie,[2] Shameem Mahmood,[1] Sajitha Sachchithanantham,[1] Helen J Lachmann,[1] Ana Martinez De Azcona Naharro,[1] Julian D Gillmore,[1] Carol J Whelan,[1] Marianna Fontana,[1] Oliver Cohen,[1] Philip N Hawkins,[1] and Ashutosh D Wechalekar[1]

[1] National Amyloidosis Centre, University College London, London, UK

[2] Biostatistics Unit, UCL Eastman Dental Institute, London, UK

Running head: ASCT: no survival benefit in amyloidosis

Author correspondence:

Professor Ashutosh Wechalekar

National Amyloidosis Centre,

University College London (Royal Free Campus)

Rowland Hill Street

London, UK

020 7433 2758

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a.wechalekar@ucl.ac.uk

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The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Significance Statement:

1. This paper suggests no difference in survival outcomes for AL patients treated with ASCT or standard chemotherapy.
2. The outcomes of patients achieving a partial/no response to transplant are inferior to those achieving a CR/VGPR with bortezomib
3. Time to next treatment appeared to be greater in the ASCT cohort with improved renal responses compared with chemotherapy.
4. We hope these findings result in further, prospective randomised controlled trials to analyse the ongoing benefit of ASCT in the era of modern chemotherapeutic agents.

Abstract:

Objectives:

The benefit of autologous stem cell transplantation (ASCT) in the treatment of light chain (AL) amyloidosis requires re-evaluation in the modern era. This retrospective case-matched study compares ASCT to bortezomib for the treatment of patients with AL amyloidosis.

Methods:

Newly diagnosed patients with AL amyloidosis treated with ASCT or bortezomib between 2001-2018 were identified. Patients were excluded if the time from diagnosis to treatment exceeded 12 months. Patients were matched on a 1:1 basis, using a propensity matched scoring approach.

Results:

A total of 136 propensity-score matched patients were included (ASCT n= 68, bortezomib n=68). There was no significant difference in overall survival at two years (p=0.908, HR: 0.95, CI:0.41-2.20). For ASCT vs. bortezomib: overall haematological response rate at six months was 90.6% vs. 92.5%; organ response at 12 months: cardiac (70.0% vs. 54%, p>0.999), renal (74% vs.24%, p=0.463)) liver (21% vs. 22%, p=0.048); median progression free survival (50 vs. 42 months p=0.058, HR:0.61, CI:0.37-1.02) and time to next treatment (68 vs. 45 months, p=0.145, HR:0.61, CI:0.31-1.19). More patients required treatment in the bortezomib group compared to ASCT group at 24 months (41 vs. 23, Chi squared p=0.004) and 48 months (57 vs 41, Chi squared p= 0.004).

Conclusions:

This small retrospective study suggests that there is no clear survival advantage of ASCT over bortezomib therapy. A prospective randomised controlled trial evaluating ASCT in AL amyloidosis is critically needed.

Key words: plasma cell neoplasms, transplantation, multiple myeloma

Introduction

High dose chemotherapy followed by autologous stem cell transplantation (ASCT) is considered to be one of most effective treatment for patients with AL amyloidosis. The median overall survival (OS) for patients who achieve a haematological complete response to ASCT is in excess of 15 years,[1] far exceeding that achieved with any standard chemotherapy based regime, but most patients with AL amyloidosis are not suitable for ASCT and so are treated with standard multi agent chemotherapy.

The median survival with oral melphalan and dexamethasone (the gold standard until recent years) is 5.1 years,[2] and the median survival with bortezomib, cyclophosphamide and dexamethasone (the current gold standard) shows a median survival of over 6 years.[3] The improved outcomes with chemotherapy have led to a long-standing debate of the benefit of ASCT over standard chemotherapy.

A case-control study conducted by Dispenzieri et.al (2004) reported a superior OS for ASCT compared to standard chemotherapy (71% vs. 41% respectively).[4] The French prospective, randomised trial (2007) contradicted this finding with a median OS 22.2 vs. 56.9 months, for ASCT compared to oral melphalan and dexamethasone therapy.[5] Since these initial studies, the transplant related mortality (TRM) associated with ASCT has dramatically decreased.[1,6] This reduction in TRM should favour ASCT over standard chemotherapy.[7] This certainly seemed to be the case in the 2016 Mayo group analysis with a superior progression free survival (PFS) (51.7% vs. 29.1%) and OS (83.6% vs. 58.8%) for ASCT vs oral melphalan and dexamethasone therapy. [8] A retrospective study (2017) also confirmed superior PFS (not reached vs. 9 months) and OS (74 months vs. 8 months) for ASCT over standard chemotherapy.[9] This is the only study to date comparing the outcomes of ASCT with patients treated with bortezomib-based therapy.

Latest data from our own centre[10] suggests that this previous study may underestimate the survival benefit with bortezomib treatment in the modern era suggesting, perhaps, that outcomes may now be comparable with ASCT. To address and resolve this ongoing controversial debate, we performed a retrospective, case-matched study of patients with AL amyloidosis treated with an ASCT versus standard bortezomib chemotherapy in the UK.

Methods

We searched our database for all newly diagnosed patients with AL amyloidosis treated with high dose chemotherapy followed by ASCT or bortezomib treatment from 1994-2018. The consort diagram in Figure 1 illustrates the selection process.

Patients were excluded if the date of ASCT preceded 2001, to allow a fair comparison of modern transplant practice with bortezomib treatment. All patients in the bortezomib arm received treatment from 2007-2018. Patients treated with bortezomib followed by an ASCT were excluded from the bortezomib arm. Patients from both treatment arms were excluded if the time from diagnosis to treatment exceeded 12 months, or if the patients were Eastern Cooperative Oncology Group performance status (ECOG) 3 or 4.

In all cases, a diagnosis of amyloidosis was confirmed by Congo red staining of a tissue biopsy with demonstration of characteristic birefringence under cross-polarized light. The amyloid subtype was confirmed by immunohistochemistry with specific antibodies, or by mass spectrometry.[11] All patients had a detailed baseline assessment of organ function with biomarker assessments and imaging including SAP scintigraphy. The bone marrow plasma cell percentage was also recorded, where available. Details of the stem cell conditioning regimen and any treatment given prior to ASCT were also recorded. Organ involvement was defined according to the international amyloidosis consensus criteria.[12] In the UK, ASCT is not recommended as first line therapy for patients with: cardiac amyloidosis with N-terminal pro-brain natriuretic peptide (NT-proBNP) >590 pmol/l (4989.63 ng/L) and/or troponin-T > 0·06 ng/ml, severe autonomic neuropathy, significant gastrointestinal bleeding due to amyloid, advanced renal failure, age over 70 years, symptomatic recurrent amyloid related pleural effusions or poor Eastern Cooperative Oncology Group performance status.

Hematological response was assessed at six months and organ responses at 12 months; both calculated from the start of bortezomib treatment, or from the date of return of stem cells for those in the ASCT group, and defined according to the international amyloidosis consensus criteria.[12] The primary outcome was overall survival (OS) defined as time from the start of bortezomib treatment/ or from day 0 of ASCT treatment, to death in months. Survival analyses were also calculated at 12, 24- and 48-months post treatment. To overcome the possible impact of early mortality (TRM or early mortality

due to cardiac disease in transplant and bortezomib arms respectively) on outcome, landmark analyses was performed at 12 months post treatment. Secondary outcomes included: progression free survival (PFS) defined as time to relapse (or progression requiring treatment), or death; time to next treatment (TTNT), defined from the date of bortezomib/ASCT to the start of next treatment; and TRM, defined as all-cause mortality before day +100, calculated from the start of bortezomib treatment or from the return of stem cells.

Statistical analysis was performed using Stata (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). Missing values were replaced by the mode if the variable was categorical, and by the median if it was numerical. Patients were then matched on a 1:1 basis using propensity scores to overcome the potential bias due to confounding in a non-randomised study.

Matched pairs were created by matching without replacement using greedy neighbor matching with a caliper distance equal to 0.2 times the pooled standard deviation of the logit of the propensity score. The variables used for the matching were all variables thought to clinically impact survival and be significant at the 5% level on univariable analysis. These variables were: age at the time of treatment, Eastern Cooperative Oncology Group performance status (ECOG), N-terminal B natriuretic peptide (NT-proBNP), bilirubin, cardiac involvement, left ventricular septal wall thickness on echocardiogram (IVS), the number of organs involved, the difference in serum free light chains >180mg/L (dFLC) and Mayo stage 2 and 3, as per the Mayo 2004 criteria.[13] Summary data were derived to show the distributions of baseline characteristics before and after propensity score analysis; the comparability of the groups before and after matching was assessed by determining the standardized mean difference (SMD) for each variable. Survival outcomes were analysed using the Cox proportion hazards model, in which treatment group was the only explanatory variable. The assumption of proportional hazards was checked and satisfied in each model and a robust variance estimator was used to account for clustering within the matched sets. All P-values were two sided and any variable with a P-value <0.05 was considered significant. Approval for analysis and publication was obtained from the institutional review board at the University

College London, and written consent was obtained from all patients in accordance with the Declaration of Helsinki.

Results

Patient baseline characteristics

A total of 81 patients undergoing ASCT and 819 patients treated with bortezomib were included in the matching procedure. The consort diagram (Fig. 1) shows the flow of patients. A total of 13/81(16%) and 751/819(84%) were excluded from the ASCT and bortezomib cohorts, respectively, after propensity matching. A total of 68 matched patients were eligible for analysis in both treatment arms after propensity score matching. The baseline patient characteristics are outlined in Table 1. There was no significant difference between the two groups using a propensity score matching approach. (Appendix table). The median plasma cell percentage at diagnosis was available in 82% of cases (n=112/136) with no significant difference between the two groups (ASCT 15% vs. bortezomib 10%, p=0.379, CI: 6.48- 16.54). Patients were treated from 2001-2018 (ASCT: 2001-2018 and bortezomib: 2007-2018). The median time from diagnosis with AL amyloidosis to treatment was <12 months for all patients (ASCT- 7 months (95% CI: 6.4-8 months) bortezmib- 2 months (95% CI 1-2 months), p <0.001.) A total of 18 patients (n=18/68, 26%) had an up-front ASCT. The remaining 52 patients, had chemotherapy prior to ASCT. (Table 1). This was: thalidomide (n=16/68, 24%), melphalan (n=3/68, 4%), lenalidomide (n=5/68, 7%), other (n=5/68, 7%) or bortezomib based (n=21/68, 31%).

Haematological response

Haematological response was assessed at six months post ASCT or bortezomib treatment and is outlined in Table 2. Haematological response was evaluable in 86% (n=117/136, ASCT n=64, bortezomib n=53); in the remaining 19 patients, 9 patients had died (ASCT=4, bortezomib=5), 5 patients had uninterpretable light chains at baseline and 5 patients had missing light chain readings. An overall haematological response, defined as a partial response or better, was achieved in 90.6% (n=58/64) of ASCT vs. 92.5% (n=49/53) of patients treated with bortezomib. A complete haematological response (CR) was achieved in 43.8% (n=28/64) vs. 30.2% (n=16/53) of patients treated with ASCT versus bortezomib alone (p=0.17).

Overall survival

The median follow-up for the entire cohort was truncated at 120 months owing to the small number of events after this time point. The median follow-up for each group was ASCT 38.5 (IQR 17-73.5 months) and bortezomib 26.5 (IQR 16-39.5 months) (Fig 2.) In this time there were 31 deaths (ASCT n=20, bortezomib n=11). Six patients had died within 100 days of return of their stem cells in the ASCT group (TRM 8.8%, n=6/68) and four patients died within 100 days of receiving their first dose of bortezomib (TRM 6%, n=4/68). At 12 months (92% vs 91%), 24 months (88% vs 85%) and 48 months (78% vs 82%) patients were alive in the ASCT and bortezomib treatment groups, respectively. To overcome the possible impact of early mortality on outcome, landmark analyses were also performed at 12, 24 and 48 months with no survival difference for either group at any of the time points. We then went on to analyse OS in both cohorts stratified depth of haematological response. The median OS was not reached by patients who achieved a CR/VGPR to treatment in either ASCT or bortezomib treated patients; patients who achieved a PR/no response to ASCT had a non-significantly longer median OS than the bortezomib treatment patients (78 months vs.60 months p=0.296, HR: 2.03, CI: 0.54-7.69).

Progression free survival and time to next treatment

A total of 71 patients relapsed or died during the follow-up period (ASCT n=30), bortezomib (n=41). The median progression free survival (PFS) was 50 months vs. 42 months in the ASCT treated versus bortezomib treated groups respectively (P=0.058, HR: 0.614, CI: 0.37-1.02) (Fig. 3). At 12 months post treatment (86% vs. 74%), 24 months (72% vs. 54%) and 48 months (51% vs. 40%) of patients had died or progressed in the ASCT and bortezomib treatment groups respectively.

Haematological response at 6 months was a highly significant predictor of PFS. For patients who achieved a CR/VGPR to ASCT or to bortezomib treatment, there was no significant difference in the PFS (p=0.409, HR: 1.35, CI: 0.66-2.77). The PFS was significantly shorter for patients who achieved a partial (PR) or no response (compared to a complete (CR) or very good partial response (VGPR)) in either group: in the ASCT group (17 months vs. 66 months, p=0.002, HR: 3.23, CI: 1.56-6.67) and bortezomib

group (11 months vs. 45 months, p<0.0001, HR: 7.72, CI: 3.48-17.10) (see Fig.4). The PFS was not significantly different between the VGPR patients when comparing either groups. There was no significant difference in the median TTNT for patients who underwent ASCT compared to bortezomib (p=0.145, HR: 0.61, CI: 0.31-1.19); there was no significant difference in the numbers requiring treatment at 12 months, (ASCT=14, bortezomib= 17, Chi squared p=0.682), but significantly more patients required treatment in the bortezomib group at 24 months (ASCT= 23, bortezomib= 41, Chi squared p=0.004) and 48 months (ASCT= 41, bortezomib =57, Chi squared p= 0.004).

Organ response

Organ response was calculated at 12 months and is outlined in Table 2. A cardiac response was evaluable in 62% (n=23/37) of patients with cardiac involvement (5 patients had died and the remaining 9 had missing NT-proBNP readings). A cardiac response was seen in 70% vs. 54%, p>0.099, of ASCT and bortezomib patients, respectively. A renal response was evaluable in 78% (n=76/97) of patients with renal involvement (5 patients had died and 16 patients had missing values). A renal response was seen in 74% vs. 24%, p=0.463, of patients in the ASCT and bortezomib groups respectively. A total of 31 patients had liver involvement and 87% (n=27/31) were evaluable (three patients had missing liver function tests and one patient had died). Of these 27 patients, 21% vs 22%, p=0.048, of patients in the ACST compared to bortezomib group had a liver response at 12 months post treatment.

Discussion

This study provides no evidence of survival advantage of ASCT compared with bortezomib based chemotherapy in patients with systemic AL amyloidosis. This is the first study to match patients with ASCT with upfront bortezomib in an unselected patient cohort. Similar haematological responses rates are seen with ASCT and bortezomib based combination regimes, and nearly half of all treated ASCT lacked a deep/complete response to treatment. Furthermore, patients achieving a less than very good partial response with ASCT seem to have worse outcomes than those patients treated with bortezomib who achieve a deeper response.

Treatment for AL amyloidosis has remarkably evolved over the last two decades. In the mid-1990's, when no novel agents were available for treatment of plasma cell disorders, use of ASCT was a crucial step and game changing progress in improving outcomes for these patients. Since then there has an ever-expanding repertoire of highly efficacious chemotherapeutic agents, with manageable treatment related toxicity. This has ultimately given both physicians and patients much greater choice. This choice is leading many clincians' to question the default option of suggesting ASCT to eligible patients.

We recently reported excellent OS and TTNT with bortezomib based chemotherapy in newly diagnosed AL amyloidosis. [10] This expands on our previous report of a smaller cohort, [3] and previous findings with oral melphalan-dexamethasone.[2] It appeared that the main advantage of ASCT – a prolonged time to disease progression and next treatment – had been eroded by this data. This has raised the old dilemma: is the true benefit of ASCT simply due to patient selection?[14]

The ideal was to address this question would be a randomised trial of transplant versus no transplant, but randomisation is very challenging with such a rare disease. Our previous study (UK amyloidosis treatment trial) attempted to address this in a randomised fashion (ASCT vs. CTD chemotherapy) but failed to recruit any patients. The current data circumvent the issue of patient recruitment. Through a carefully matched data set, the median OS was not significantly different between ASCT vs. bortezomib treated cohorts. The PFS was also not significantly different. A landmark analysis, to overcome

any bias of transplant related mortality or early cardiac also confirmed essentially similar OS and PFS values for both groups.

The importance of haematological response in AL amyloidosis is already well described.[15,16] Both the cohorts in this study confirmed that patients achieving a CR/VGPR had excellent outcomes compared to those in a partial/no response. Although a higher proportion of patients achieved a CR with transplant compared with bortezomib based chemotherapy, this was not statistically significant and the outcomes of patients with CR or VGPR in either group (ASCT vs. bortezomib) were similar. The outcomes of patients achieving a partial/no response to transplant were clearly inferior to those achieving a CR/VGPR with bortezomib, and remained comparable to those achieving PR or less with bortezomib. This suggests that, if a CR/VGPR is reached, treatment modality does not appear to influence survival outcome, and, conversely, any patient with a poor response has a worse outcome, regardless of the treatment type. The problem then becomes an issue of patient selection based on the risk and morbidity of treatment. The treatment related mortality in both cohorts in this study was similar, the intangible factors in ASCT – careful patient selection, experience of the transplant centre, the exact selection criteria – become critically important.

Even though there was no evidence of survival advantage in this group of patients with ASCT over chemotherapy, there were two notable finding in favour of ASCT. The time to next treatment appeared to be greater in the ASCT cohort compared with bortezomib based regimes, with significantly fewer patients requiring treatment at 24 and 48 months. The other notable finding was the apparently better renal responses with ASCT compared with chemotherapy. This is difficult to reconcile but may well depend on patient selection. Patients with very advance renal dysfunction or low albumin (<25g/L) are not selected for ASCT in the UK and so this may difference may simply reflect a bias towards limited organ involvement in the ASCT group allowing organ function improvement. It would be important to have a pooled international analysis to assess and confirm this finding.

We acknowledge that this study has limitations. This is a retrospective case-matched analysis and some variables had missing data. There were no baseline cytogenetic data, and we are aware that patients with t(11;14) or del1q have reportedly better outcomes

with ASCT.[18] Despite extensive efforts to match patients, there are differences between the cohorts. Bortezomib patients were treated at a slightly later time period, (2007 onwards) compared with the ASCT patients (2001 onwards). Although, the majority of patients were transplanted after 2007 (57/68, 84%), 11 patients (11/68, 16%) were transplanted before 2007. This may have negatively influenced outcomes for the ASCT arm as improvements in survival in AL amyloidosis treatments will have occurred in the six years from 2001-2006. Also assessing survival outcomes at two years may arguably be too short a period of time for any significant survival benefit to be noted.

Despite these limitations, this paper outlines comparable survival outcomes for ASCT and bortezomib. This data focused on patients treated with ASCT within the first year of diagnosis. We recently reported the outcomes of consolidation transplant in patients ineligible for ASCT at presentation but who improved after chemotherapy.[17] This needs to be explored further and may suggest an alternative place/ role for ACST in a patients' treatment trajectory.

In conclusion this case-control study provides no evidence of a difference in survival outcomes (overall or progression free survival) for patients with AL amyloidosis treated with ASCT compared with standard bortezomib therapy. Deep haematological and organ responses can be achieved with both treatments. Patients who do not achieve an adequate clonal response to ASCT have inferior outcomes when compared to patients who achieve a good haematological response with standard bortezomib therapy. It is of paramount importance that these findings are confirmed in a larger cohort with international collaboration of patients treated in the contemporary period.

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Figure legends

Figure 1: Consort diagram to outline the selection of patients in both the autologous stem cell transplant and bortezomib treatment groups

Figure 2: Overall survival in patients with AL amyloidosis treated with autologous stem cell transplant compared with bortezomib (Velcade) alone

Figure 3: Progression free survival in patients with AL amyloidosis treated with autologous stem cell transplant compared with bortezomib (Velcade) alone

Figure 4: Time to next treatment in patients with AL amyloidosis treated with autologous stem cell transplant compared with bortezomib (Velcade) alone, stratified by haematological response (complete response/very good partial response versus other response).

Appendix

Table 1: standardised differences of the variables used in matching to demonstrate the effect of propensity scoring matching between the bortezomib and ASCT groups.

Variable **N/median, (range/%)**	**Bortezomib (n=68)** Mean/n (sd/%)	**ASCT (n=68)** n(%)/median(range)	**Standardised difference to test matching***
Performance Status			
0	29 (42.6)	26 (38.2)	0.10
1	34 (50.0)	36 (52.9)	
2	5 (7.4)	6 (8.8)	
Mayo Stage			
1	37 (54.4)	38 (55.9)	0.13
2	26 (38.2)	23 (33.8)	
3	5 (7.4)	7 (10.3)	
Organ Involvement			
Heart	0.26 (0.44)	0.279	-0.03
Number of organs involved(median)			0.30
1	39 (57.4)	43 (63.2)	
2	23 (33.8)	17 (25.0)	
3	4 (5.9)	7 (10.3)	
4	1 (1.5)	1 (1.5)	
5	1 (1.5)	0 (0)	
dFLC >180mg/l	0.397 (0.49)	0.43 (0.50)	-0.06
Age at treatment (years)	59.87 (9.13)	58.29 (6.58)	0.20
IVS (mm)	11.03 (2.05)	11.35 (1.98)	-0.16
NT-proBNP (ng/L)	2.56 (1203.7)	884.8 (1320)	-0.03
TnT	28.46 (28.54)	19.33 (27.05)	0.32
Bilirubin (µmol/l)	5.78 (3.87)	6.65 (2.94)	-0.25
ALP (IU/l)	118.2 (115.67)	88.82 (55.53)	0.32

IVS= left ventricular septal thickness; dFLC= difference in serum free light chains; NT-proBNP = N-terminal B natriuretic peptide; TnT= high sensitivity cardiac troponin; ALP= alkaline phosphatase.

*The standardised difference compares the difference in means in units of the pooled standard deviation. There is no universally agreed criterion as to what threshold of the standardised difference can be used to indicate important imbalance, but a difference less than 0.1 has been taken to indicate a negligible difference in the mean or prevalence of a covariate between treatment groups.

Table 1: a comparison of patient baseline characteristics between patients treated with ASCT and bortezomib

Variable **N/median, (range/%)**	**Bortezomib (n=68)** n(%)/median(range or mean (range)	**ASCT (n=68)** n(%)/median(range) or mean(range)
Age at treatment (years)	59.9 (40-75)	58.5 (57-61)
Year of diagnosis		
2000-2004	0	10 (14.7)
2005-2008	0	8 (11.8)
2009-2012	4 (58.8)	16 (23.5)
2013-2017	64 (94.1)	34 (50)
Gender (male)	42 (56)	323 (44.0)
Performance Status		
0	29(42.6)	26(38.2)
1	34(50)	36(52.9)
2	5(7.4)	6(8.8)
Mayo Stage		
1	37(54.4)	38(55.9)
2	26(38.2)	23(33.8)
3	5(7.4)	7(10.2)
No. of organs involved	1 (1-5)	1 (1-4)
Organ Involvement		
Heart	18(20)	19 (20.4)
Kidney	51 (55.4)	46 (49.5)
Liver	10 (10.9)	21 (22.6)
GI	0 (0)	2 (2.2)
Peripheral NS	7 (7.6)	4 (4.3)
Autonomic NS	6 (6.5)	1 (1.1)
dFLC(mg/L)	139.5(0-5316)	170.1.(5.3-26697)
BM PC % (median)	10 (1-80)	15 (1-90)
Treatment prior to ASCT	/	13 (19.1)
Thalidomide		1 (1.5)

Lenalidomide Melphalan Bortezomib (patients excluded from bortezomib arm) Other Nil		2 (2.9) 23 (33.8) 11 (16.2) 18 (26.5)
IVS (mm)	11 (10-11)	11 (10-12)
NT-proBNP (ng/L)	273.1 (203.6-439.3)	381.4 (263.7-549.4)
TnT (ng/ml.)	21 (17-26)	9.5(9.5-12)
Baseline creatinine (µmol/l)	123.7 (40-979)	90.2(34-476)
eGFR (mls/min)	72.6 (10-100)	79.0 (15-90)
Albumin (g/l)	32.9 (19-53)	33.6 (17-46)
Proteinuria (g/24hr)	5.4 (0.1-23.2)	4.5 (0.05-14.8)
Bilirubin (µmol/l)	5 (4-5)	6 (6-6)
ALP (IU/l)	80.5 (74-92.4)	79.8.(4-86.6)
6 min walk test (m)	457.9 (92-656)	470.1 (141-697)

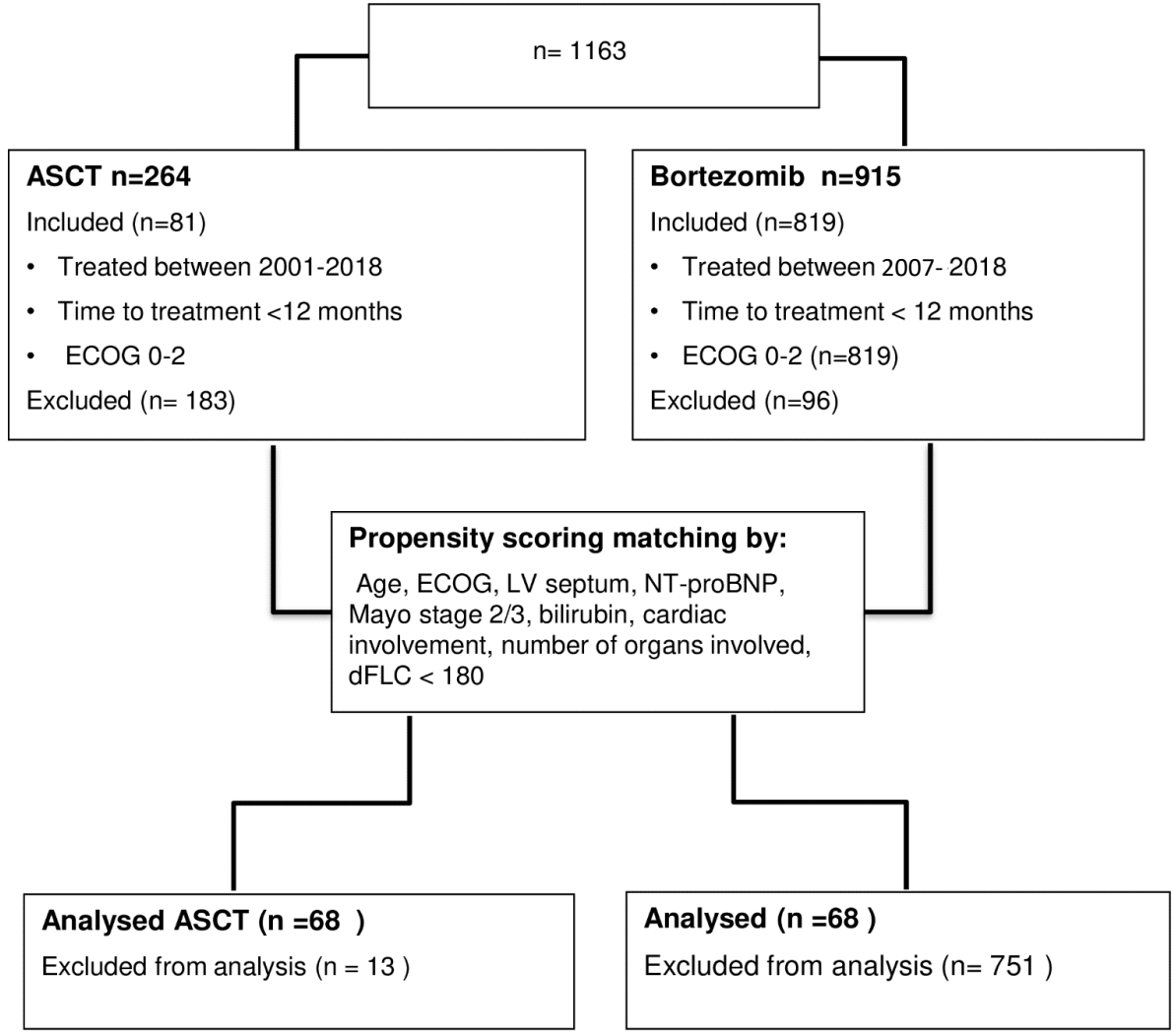
GI= gastrointestinal; NS= nervous system; IVS= left ventricular septal thickness; dFLC= difference in serum free light chains; NT-proBNP = N-terminal B natriuretic peptide; TnT= high sensitivity cardiac troponin; eGFR= estimated glomerular filtration rate; ALP= alkaline phosphatase; CI= confidence interval; BM= bone marrow; PC= plasma cell.

Table 2: a comparison of haematological and organ responses for patients treated with ASCT and bortezomib

Response	**All (n=136)**	**Bortezomib n=68 n (%)**	**ASCT n=68 n (%)**
Haematological response	(n=126)	(n=53)	(n=68)
Complete response	44 (34.9)	16 (30.2)	28 (41.2)
Very good partial response	33 (26.2)	19 (32.8)	14 (20.6)
Partial response	30 (23.8)	14 (24.1)	16 (23.5)
No response	17 (13.5)	5 (9.4)	4 (5.9)
Progressive disease	2 (1.7)	0 (0)	2 (2.9)

Cardiac response (evaluable n=23)	(n=23)	(n=13)	(n=10)
Response	14 (60.9)	7 (53.8)	7 (70)
No response/progression	9 (39.1)	6 (46.2)	3 (30)
Renal response (evaluable n=76)	(n=76)	(n=37)	(n=39)
Response	38 (50)	9 (24.3)	29 (74.3)
No response/progression	38 (50)	28 (75.7)	10 (25.6)
Liver response (evaluable n= 27)	(n=27)	(n=9)	(n=28)
Response	8 (29.6)	2 (22.2)	6 (21.4)
No response/progression	19 (70.4)	7 (77.8)	12 (42.9)

ASCT= autologous stem cell transplant



ASCT=autologous stem cell transplant; ECOG= Eastern Cooperative Oncology Group performance status; NT-proBNP= N-terminal B natriuretic peptide; LV= left ventricle; dFLC= difference between involved and uninvolved light chains.

Figure 2

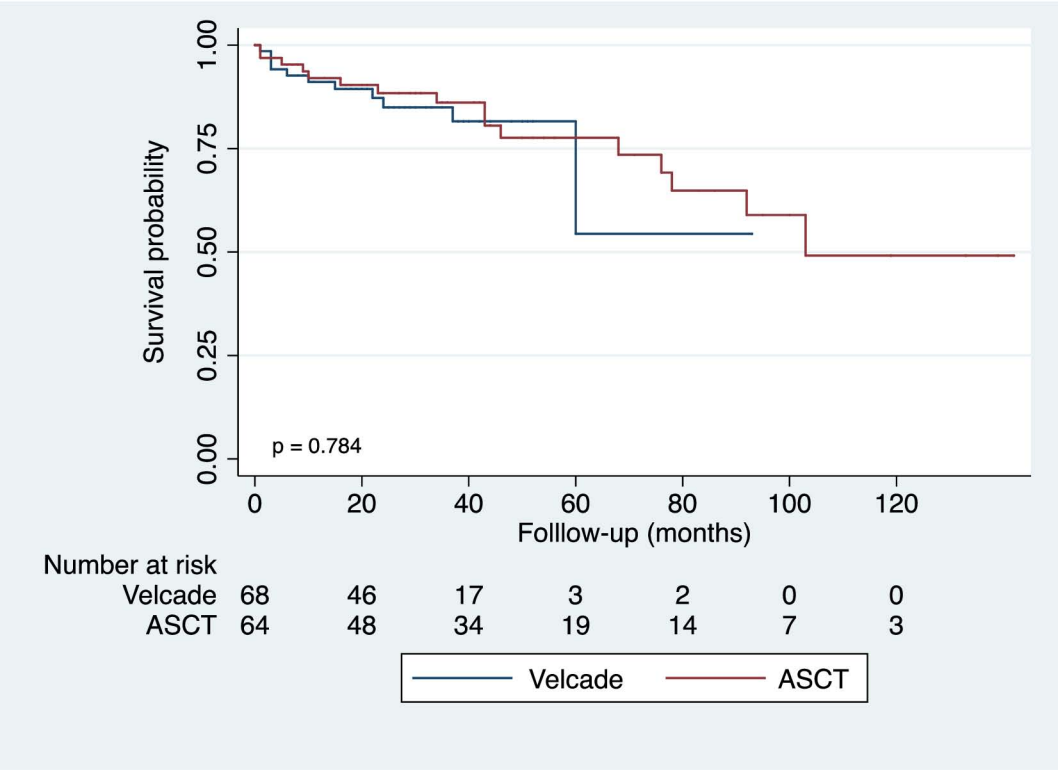

Survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.784
0
20
40
60
80
100
120
Folllow-up (months)
Number at risk
Velcade 68 46 17 3 2 0 0
ASCT 64 48 34 19 14 7 3
Velcade
ASCT

Figure 3

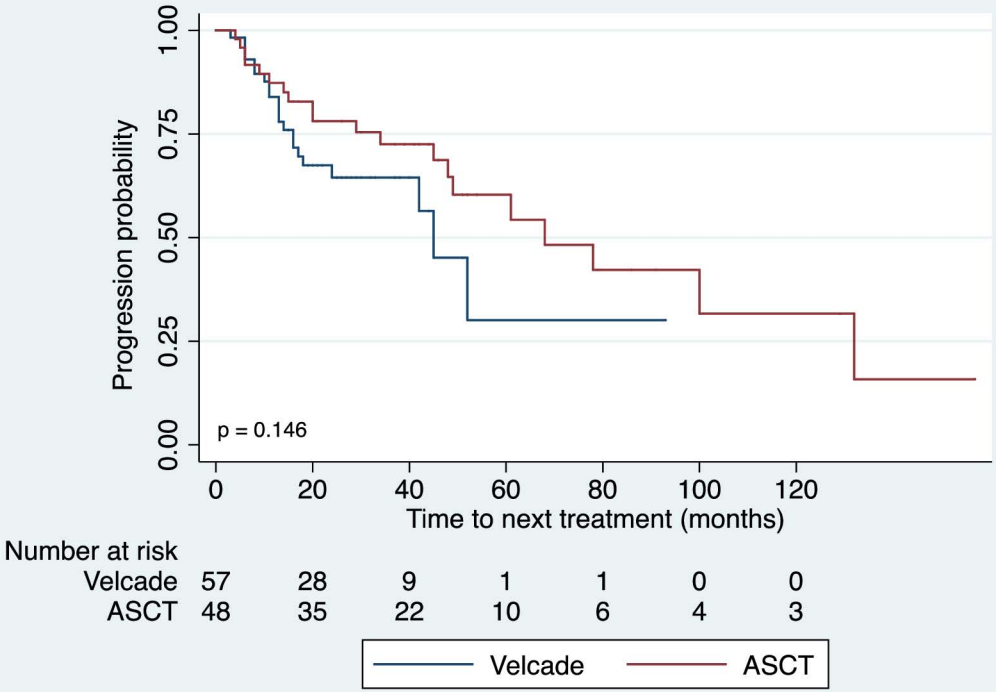
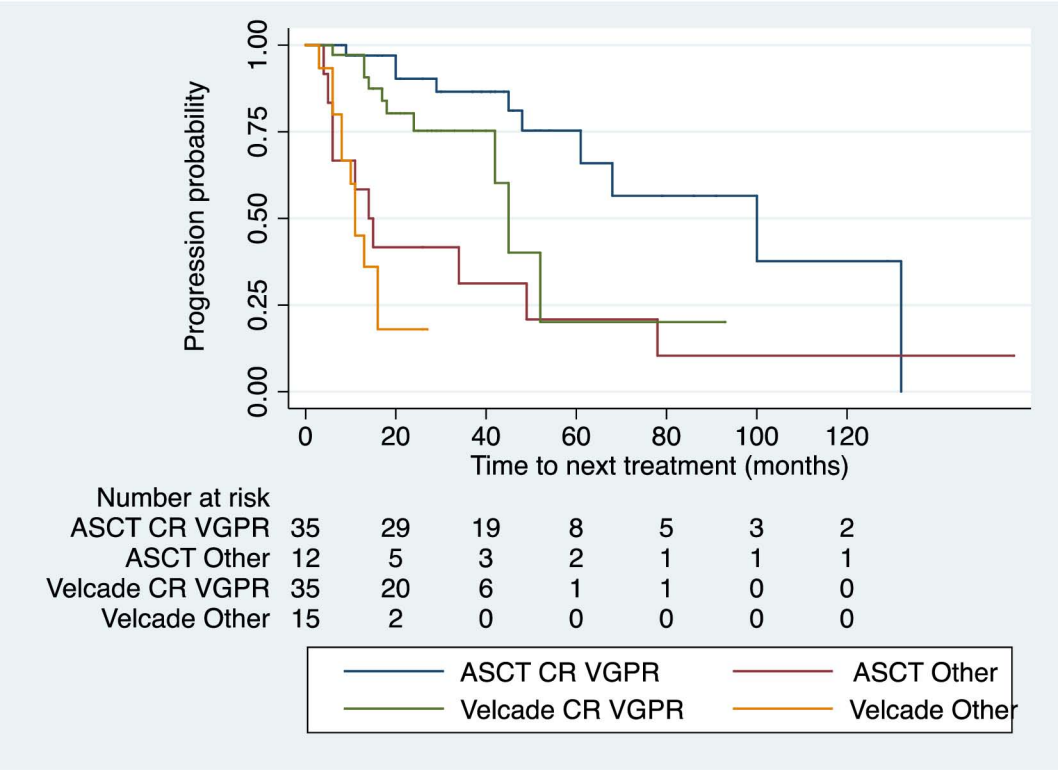

Progression probability
1.00
0.75
0.50
0.25
0.00
p = 0.146
0
20
40
60
80
100
120
Time to next treatment (months)
Number at risk
Velcade 57 28 9 1 1 0 0
ASCT 48 35 22 10 6 4 3
Velcade
ASCT

Figure 4


Progression probability
0.00
0.25
0.50
0.75
1.00
0
20
40
60
80
100
120
Time to next treatment (months)
Number at risk
ASCT CR VGPR 35 29 19 8 5 3 2
ASCT Other 12 5 3 2 1 1 1
Velcade CR VGPR 35 20 6 1 1 0 0
Velcade Other 15 2 0 0 0 0 0
ASCT CR VGPR
ASCT Other
Velcade CR VGPR
Velcade Other