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Chromosome 1 Abnormalities Predict Shortened Progression Free and Overall Survival in Patients with High Risk Multiple Myeloma Undergoing Autologous Hematopoietic Cell Transplantation, a Retrospective Analysis

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Abstract

Abnormalities of chromosome (ch)1 have been shown to be significant adverse prognostic factors in multiple myeloma (MM) but they have not yet been systematically studied in patients undergoing autologous hematopoietic cell transplantation (auto-HCT). The aim of this study was to determine whether patients with high-risk MM and ch1 abnormalities (1q gain, 1p deletion, translocations of ch1) constitute a highest risk group compared to a contemporaneous cohort of high-risk MM patients without ch1 abnormalities. 232 patients (169 induction, 63 salvage) with MM and at least one recognized high-risk feature met criteria for inclusion. The presence of a ch1 abnormality (n=15) was highly significant in patients undergoing salvage autologous HCT (n=6) for predicting shorter PFS (p<0.001; HR= 22.93; 95% CI: 4.94- 106.48), and OS (p = 0.0002; HR= 21.22; 95% CI: 1.18-14.98). Median PFS and OS for those with a ch1 abnormality and del 13q (n=7) were 4.76 and 9.43 months, with ch1 abnormality and no del 13q (n=8) were 16.79 and 35.22 months respectively, and for those Without cytogenetic abnormalities, 24.44 and 57.03 months respectively. Based upon the impact of ch1 abnormalities on auto-HCT outcomes in this study, further investigation in larger series is warranted.

Keywords: Multiple myeloma; Chromosome 1; Stem cell transplant

Introduction

Abnormalities of chromosome 1 (ch1) are common in hematological malignancies and are among the most common structural aberrations found in MM [1,2]. Abnormalities of both the long arm (1q gain) and short arm (1p loss) have been shown to be significant adverse prognostic factors in myeloma [3-8] but they have not yet been included in the new IMWG molecular cytogenetic classification [9], or other large myeloma centers' prognostic criteria such as the Mayo Clinic mSMART criteria [10].

However, according to the 2014 NCCN guidelines, the FISH panel for prognostic estimation should also include ch1 amplification [11].

The literature contains several small cohorts limited to one or few institutions and some studies have failed to confirm the overriding negative prognostic association with ch1 amplification detected by FISH, thus controversy regarding the impact of ch1 abnormalities exists [6,12]. In particular, the impact of ch1 abnormalities on auto-HCT outcomes has been associated with adverse survival [13,14], but has not been widely or systematically studied.

Regarding specific ch1 aberrations encountered, the short arm of ch1 is most often associated with deletions and the long arm of ch1 with amplifications. The majority of these abnormalities involve rearrangements located in the peri-centromeric regions and frequently in the form of jumping translocations.

One of the genes mapped at 1q21 is CKS1B, a member of the highly conserved cyclin kinase subunit 1 (CKS1) protein family that interacts with cyclin dependent kinases (Cdks) and plays a critical role in cell cycle progression [15].

CKS1 is an essential cofactor for efficient Skp2-dependent ubiquitination of p27Kip1 [16]. CKS1B overexpression is correlated

with low p27 expression and adverse survival in several human malignancies.

Its presence in MM is associated with a higher risk of progression and the incidence is higher in relapsed than in newly diagnosed patients [17]. Although less commonly described, deletions of CDKN2C at 1p32 impact G1/S transition resulting in poor outcomes [13].

The aim of this study was to describe MM patients with any high risk characteristic that underwent auto-HCT and to compare outcomes between various high risk groups. Specifically, we aimed to identify whether ch1 abnormalities (including 1q gain, 1p deletion and translocations of chromosome 1 with other partners) constituted a 'highest' risk group that may benefit from investigation of alternative treatment strategies in future studies.

Patients and Methods

A retrospective cohort study of MM patients with any high risk feature, who received an auto-HCT as induction or salvage treatment at OHSU between 01/01/2001 and 12/31/2011 was performed after

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obtaining Institutional Review Board approval in keeping with the declaration of Helsinki.

Subjects were identified using the CIBMTR database, institutional databases as well as from individual patient medical records. High risk features are defined as cytogenetically detected deletion (del) 13, cytogenetically detected chromosome 1 abnormality, cytogenetic or FISH detection of del 17p, t (4;14)(p16;q32), t(14;16)(q32;q23), t(14;20)(q32;q11); plasmablastic or anaplastic morphology, multiple extramedullary plasmacytomas, achieving less than a partial remission with 2 consecutive lines of therapy, International Staging 112 System (ISS) stages II and III, Salmon-Durie staging system stages 2 and 3.

These particular features were included due to the wide acceptance of their significance in the literature. Subjects with standard or good risk cytogenetics or FISH profiles; ISS stage 1 and S-D category 1 were excluded if they did not have a co-existing high risk feature.

To delineate the impact of different genomic groups on PFS and OS, the following groups were formed based on cytogenetic and or FISH findings: group 1 (no abnormality), group 2 comprised all other well-known poor risk cytogenetic factors (del 13q by cytogenetics, t (4;14), t (14;16), t (14;20), del 17p), group 3 comprised of chromosome 1 abnormalities (that occur alone or together with other genomic abnormalities except del 13q) and group 4 comprised of chromosome 1 abnormalities occurring together with del 13q by cytogenetics).

These particular groups were formed to compare well known high and standard risk genomic profiles to those with ch1 abnormalities. The co-occurrence of ch1 abnormalities with del 13q deletion was most common and we thus decided to explore the significance of this relationship by creating group 4.

Statistical Analysis

Descriptive statistical analysis was conducted to summarize overall response rate, relapse rate, progression free survival (PFS), overall survival (OS), patients' individual and clinical characteristics and cytogenetic and FISH profiles, pre-HSCT treatment regimens and post- HSCT maintenance therapy.

PFS, OS and the time to relapse were all calculated from the date of stem cell infusion until the date of progression or death. Patients alive without progression were censored on the date of last follow up for PFS. OS was until the date of death due to any cause and living patients were censored on the last follow up date the patient was known to be alive.

Kaplan-Meier method was used to estimate the distribution of PFS and OS. A log-rank test was used to assess whether the survival function differed across the groups [18]. Univariable and multivariable logistic regression models were fitted to assess the association between overall response rate/relapse rate and risk factors measured prior to the time of transplant.

Univariable and multivariable cox regression models were fitted to evaluate the association between each of the survival endpoints (PFS and OS) and the set of covariates that are the same for the logistic regression models. Final multivariable models were determined based on Akaike's information criterion (AIC) in combination with clinical judgment. Results were considered significant if the P-value was less than or equal to 0.05. The statistical analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 232 subjects were identified and analyzed for this study. Patient characteristics, high risk features, pre-auto-HCT treatment regimens, indication for auto-HCT, pre-auto-HCT treatment characteristics and post-auto-HCT maintenance therapies are listed in (Table 1).

A total of 207 subjects had cytogenetic and/or FISH results. Among the 207 subjects, 55 received a salvage transplant and 152 an induction transplant. Among these, chromosome 1 abnormalities were detected by routine cytogenetic testing in six subjects that underwent salvage transplant and nine subjects that underwent induction transplant. There were 3 balanced translocations, 3 losses of 1q, 6 losses of 1p, 2 gains of 1q and 1 balanced translocation with gain of 1q (Table 2).

Treatment Characteristics

Stem cell transplant

One auto-HCT per patient was included for analysis. Five subjects underwent a tandem induction auto-HCT. In any single patient, if two transplants were performed (n=12), the second (salvage) transplant was included for analysis. The preparative regimen was Melphalan 200 mg/m².

Pre-transplant induction therapy

Details of the pre-transplant chemotherapy regimens were available in 203 patients. The median number of pre-transplant therapy was 2 (range 1-9).

Post-transplant maintenance therapy

Details of post auto-HCT maintenance therapy were available in 152 patients. The majority (95 patients) did not receive maintenance therapy, while 27 received lenalidomide, 3 bortezomib, 11 steroids and 16 received thalidomide.

Response and relapse rates post auto-HCT

Using the International Working Group 183 Criteria, overall response rate (ORR) for the whole group was 81.0% (95% CI: 75.4-85.9).

Complete remission (CR) occurred in 33.2%, very good partial remission (VGPR) in 31.9%, partial remission (PR) in 16.0%, minor response (MR) in 1.3%, stable disease (SD) in 5.2%, progressive disease (PD) in 5.2%.

The best response was unknown in 6.0% of cases. (Table 3) demonstrates results for induction and salvage cohorts.

Progression free and overall survival

With a median follow up of 44.5 months, 80 (34.5%) patients in this cohort had died. Among all patients who had valid relapsing information 105 (54.4%, 193 95% CI: 38.4-52.9) had relapsed disease.

For the entire group, median PFS and OS was 22.0 (95% CI: 19.5, 29.4) and 51.8 (95% CI: 35.2, 63.4) months respectively.

The 2 and 5-year PFS rates were 61.2% (95% CI: 54.9, 67.5) and 51.7% (95% CI: 45.3, 58.2) respectively.

The 2 and 5 year OS rates were 81.5% (95% CI: 76.5, 86.5) and 69.4% (95% CI: 63.5, 75.3). (Table 2) demonstrates corresponding results for induction and salvage cohorts.

Total number of subjects n	232	
Age at transplantation (years) median (range)		60(30-79)
Gender: n (%)	Male	151(65.1)
	Female	81(34.9)
ISS Stage: (n=168)	I	168 50 (29.8)
	II	75(44.64)
	III	43(25.6)
Salmon-Durie Stage: (n=167)	I	167 3 (1.8)
	II	46 (27.5)
	III	118 (70.7)
Genetic abnormality: (n=207)	del(13q) cytogenetics	207 20 (9.7)
	t(4;14)	19(9.2)
	del(17p)	13(6.3)
	t(14;16)	3(1.4)
	t(14;20)	1(0.5)
	chromosome 1 abnormality	15(7.3)
no abnormality	154(74.4)	
Plasmablastic morphology: n(%)		6(2.6)
Multiple extra medullary plasmacytomas: n(%)		14(6.0)
Prior therapies median (range)		2(0-9)
Pre- transplant regimens (n=204)	Bortezomib containing	86 (42.1)
	Lenalidomide containing	69 (33.8)
	VRD	16 (7.8)
	VAD	64 (31.4)
	Thalidomide containing	63 (30.9)
	Doxil containing	15 (7.4)
	HyperCVAD	9 (4.4)
	DCEP	5(2.6)
Cyclophosphamide containing	12 (5.9)	
<PR to 2 conventional lines of therapy prior to HSCT: n (%)		18(7.8)
Indication for auto- HCT: n (%)	Induction	232
	Salvage	169 (72.8) 63 (27.2)
Maintenance: n (%)	None	152 95 (62.1)
	Lenalidomide	26(17.1)
	Bortezomib	3 (2.0)
	Steroids	10(6.6)
	Thalidomide	16(10.5)

Table 1: Patient and clinical characteristics N=232. Abbreviations: ISS (International Staging System); t (translocation); Bortezomib, lenalidomide and dexamethasone (VRD); vincristine, adriamycin, dexamethasone (VAD); fractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone (Hyper CVAD), dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP), Del (deletion).

Univariable and multivariable analyses of high risk factors associated with shorter PFS and OS

Cox regression models were fitted for each variable listed in (Table 1). The presence of a ch1 abnormality and achieving less than a PR with 2 consecutive lines of therapy prior to transplant were statistically the most significant factors independently associated with shorter PFS and OS in this cohort of high risk subjects.

The ISS and Salmon-Durie staging 206 systems, increased number of prior therapies, del 17 p, t(4;14), t(14;16), t(14;20), del

13q by cytogenetics, multiple (>2) extramedullary plasmacytomas, plasmablastic morphology were not significantly independently associated with shorter PFS or OS in this cohort of high risk patients (Table 4).

The final multivariable models for PFS for salvage ASCT found chromosome 1 (HR 22.93; p<0.001; 95% CI:4.94-106.47) and Salmon

	Chromosome 1 abnormality		Complete cytogenetic report	
1	Balanced translocation	t(1;10)	47,X,-X,t(1;10)(q21;q26),+5,der(5)t(5;8)(p13;q13),+7,der(8)t(5;8)(p13;q13)add(5)(p15),add(12)(p1?2),add(13)(q2?2),del(14)(q24),t(14;17)(q11.2;p11.2),add(15)(q2?1),+19,-20[2]/46,XX[25]	Salvage
2		t(1;10)	49-51,X,-X,t(1;10)(p13;q24),+5,add(8)(q22),+9,-13,add(14)(q32),+15,+15,+16,+19,+21[cp4]/46,XX[15]	Induction
3		t(1;14)	Not available	Induction
4	Loss of 1q	1q12 t(1;19)	51,X,-X,del(1)(q12),+del(1),-2,+3,+5,+7,+add(9)(p?22),-13,+15,+der(19)t(1;19)(q21;p13.3)x2[1]/46,XX[24]	Salvage
5		1q32	52,XX,del(1)(q32),+3,der(3)t(3;?) (q12;?),del(5)(q31),+6,-7,+9,del(12)(p12),-13,+15,+15,der(16)add(16)(p11.2)del(16)(q24),add(17)(p11.2),+21,+mar[cp4]/46,XX[21]	Induction
6		1q43 1q32	44,X,der(X;1)t(p11.2;p36.3)del(X)(p11.2)add(1)(q43),del(1)(q32),del(2)(p23),-3,del(6)(q11.2q11.2),del(10)(p11.2p14),add(11)(q23),del(13)(q14q22)x2,add(14)(q32),-15,add(16)(p11.2),add(17)(p11.2),-18,add(20)(p12),-21,-22,+3mar[5]	Induction
7	Loss of 1p	1p13-p32	52,XY,del(1)(?p32?13),dic(1;11)(p?13;q?25),+5,add(6)(q?15),+del(6)(p22),+6,+7,-8,+9,-11,add(12)(p1?1.2),del(13)(q?14),+15,add(16)(q2?4),+18,+19,+21,-22[cp5]/46,XY[14]	Salvage
8		1p13	41-42,X,-Y,add(1)(p13),+der(3)t(3;8)(p1?1;q1?2),add(4)(q2?5),add(5)(p1?2),add(6)(q1?2),-8,+11,-13,add(13)(p11.1),-14,der(16)t(16;17)(q12-13;q1?1.2),-17,-18,+mar1[cp3]/46-49,idem,-add(1)(p13),+6,-add(6)(q1?2),+7,+add(8)(q?21),+11,-add(13)(p11.2),+del(13)(q1?2q22),+14,+15[cp7]/46,XY[10]	Salvage
9		1p36.1 1p22	40,X,-X,add(1)(p3?6.1),add(1)(p?22),add(2)(p?13),-5,add(6)(p22),-8,add(9)(q?32),-13,-13,add(16)(p?11.2),add(21)(q22),-22,add(22)(q13)[cp6]/46,XX[24]	Induction
10		1p22 1p22	49,X,-Y,add(1)(p?22),+add(1)(p?22),del(8)(q?13q22),+11,-13,+15,-18,+21,+1-3mar[cp14]/46,XY[11]	Induction
11	Loss of 1p and gain of 1q	1p13-p21 1q12	43,-X,der(X)t(X;5)(q22;p13),del(1)(p?21p?13),add(4)(p13),der(5)t(X;5)(q22;p13)add(5)(q31),del(6)(q?21q2?5),der(7)t(1;7)(q12;p15)t(7;21)(q11.2;q22),add(9)(q34),-10,del(13)(q12q14),-14,add(14)(q?24),del(18)(q21),-20,der(21)t(7;21)(q11.2;q22),+mar[6]/86,idemx2[2]/46,XX[22]	Induction

12	Loss of 1p	1p13 1p13	56,XX,+add(1)(p13),+add(1)(p13),+3,+5,+5,+6,+7,-8,+9,+9,+add(11)(p11.2),-13,-14,+15,-16,+19,-22,+mar1,+mar2,+mar3[2]/46,XX[23]	Induction
13	Gain of 1q	1q10	41,X,-Y,i(1)(q10),der(2)t(2;7)(p?23;p?15),add(4)(q25),add(4)(p?12),add(5)(q31),-7,-8,+add(12)(q15),+add(12)(q15),-13,-14,+add(15)(q26),add(15)(p11),-16,del(16)(p13),-20,+mar[1]/41,X,-Y,i(1)(q10),der(2)t(2;7)(p?23;p?15),add(4)(q25),add(4)(p?12),add(5)(q31),-7,-8,del(11)(q21),add(11)(q?23),add(12)(q?15),add(15)(q26),add(15)(p11),del(16)(p13),-16,del(19)(p11),del(19)(q13),add(20)(p11)+mar[cp2]/46,XY[19]	Salvage
14	Gain of 1q and balanced translocation	1q24 t(1;8)	52,X,add(X)(q2?6),t(1;8)(p?21;q24),+5,+6,del(6)(q13q23)x2,+7,+9,+15,+19[cp6]/60,XX,t(1;8)(p?21;q24),+der(1)t(1;8)(p?21;q24),+2,+3,+5,+6,+7,+add(7)(p1?3),+9,+9,+15,+15,+18,+19,+20[3]/46,XX[23]	Salvage
15	Gain of 1q and Gain of 1p	1q10 1p10	40-46,-X,add(X)(q25),+1,dic(1;4)(p33;q31),ins(1;?)(q25;?),del(6)(q21),del(8)(q?22),del(11)(q13q23),add(11)(q23),-13,-16,+add(17)(q23),-18,-22,+1~5mar[cp11]/46,XX[15]	Induction

Table 2: Chromosome 1 abnormalities. N = 15 (6 induction, 9 salvage). Gains or losses of long or short arms of chromosome 1 and balanced translocations.

	Induction	Salvage
Sample size	169	63
Median overall survival	57.0months (95% CI: 44.3, 70.3)	30.0 months (95% CI: 21.4,...)*
Median PFS	27.3 months (95% CI: 20.1, 37.8)	18.1 months (95% CI: 10.8, 21.9)
Relapse rate	52.48% (95% CI: 43.9, 60.9; n =141)	59.6(95% CI: 45.1, 73.0; n= 52)
Overall response	82.3% (95% CI: 75.6, 87.7)	77.8% (95% CI: 65.5, 87.3)
2-year PFS	65.1% (95% CI: 57.4, 72.3)	50.8% (95% CI: 37.9, 63.6)
5-year PFS	53.9% (95% CI: 46.0, 61.5)	46.0%(95% CI: 33.4, 59.1)
2-year OS	84.0% (95% CI: 77.6, 89.2)	74.6%(95% CI: 62.1, 84.7)
5-year OS	70.4% (95% CI: 62.9, 77.2)	66.7%(95% CI: 53.7, 78.1)

Table 3: Response rates and survival outcomes in subjects with high risk features that received an autologous stem cell transplant divided by indication: induction and salvage. *Indicates that upper bound of the confidence interval is not computable.

Durie (SD)stage III (HR 2.50; p = 0.0538; 95% CI: 0.985 – 6.349) to be significant factors.

Similarly these factors were significantly associated with shortened OS214 chromosome 1 (HR 21.218; p= 0.0002; 95% CI: 4.311-104.435) and S-D stage III (HR 4.212; p = 0.0264; 95% CI:1.184- 14.983).

The final multivariable model for the induction cohort found that none of the potential risk factors independently or jointly predict shortened PFS or OS.

Gene Variable

As the ch 1 abnormality is significantly associated with both PFS and OS, we created a variable named ‘gene variable’ consisting of the following groups: 1) no cytogenetic or FISH abnormality; 2) t (4;14) OR del 17p OR cytogenetically detected del 13q OR OR t(14;16) OR

t(14;20) a combination of these abnormalities; 3) ch1 abnormality alone OR with any other abnormality except del 13q and 4) the occurrence of both a ch1 and del 13q abnormality.

We compared the PFS and OS of these 4 groups. As there is no significant interaction present between gene variable and induction type, we report the aggregated association between the gene variable and survival outcome (PFS and OS).

Those with both a ch1 abnormality and 229 cytogenetically detected del 13q had the shortest median PFS and OS followed by those with a ch1 abnormality alone or with 230 another genetic abnormality, followed by group 2, followed by those without any cytogenetic or FISH abnormality.

The log rank test for PFS and OS across gene variable groups both had a p value of <0.0001 (Table 5 and Figures 1 and 2).

Univariable and multivariable analyses of high risk factors associated with overall response rate and relapse rate

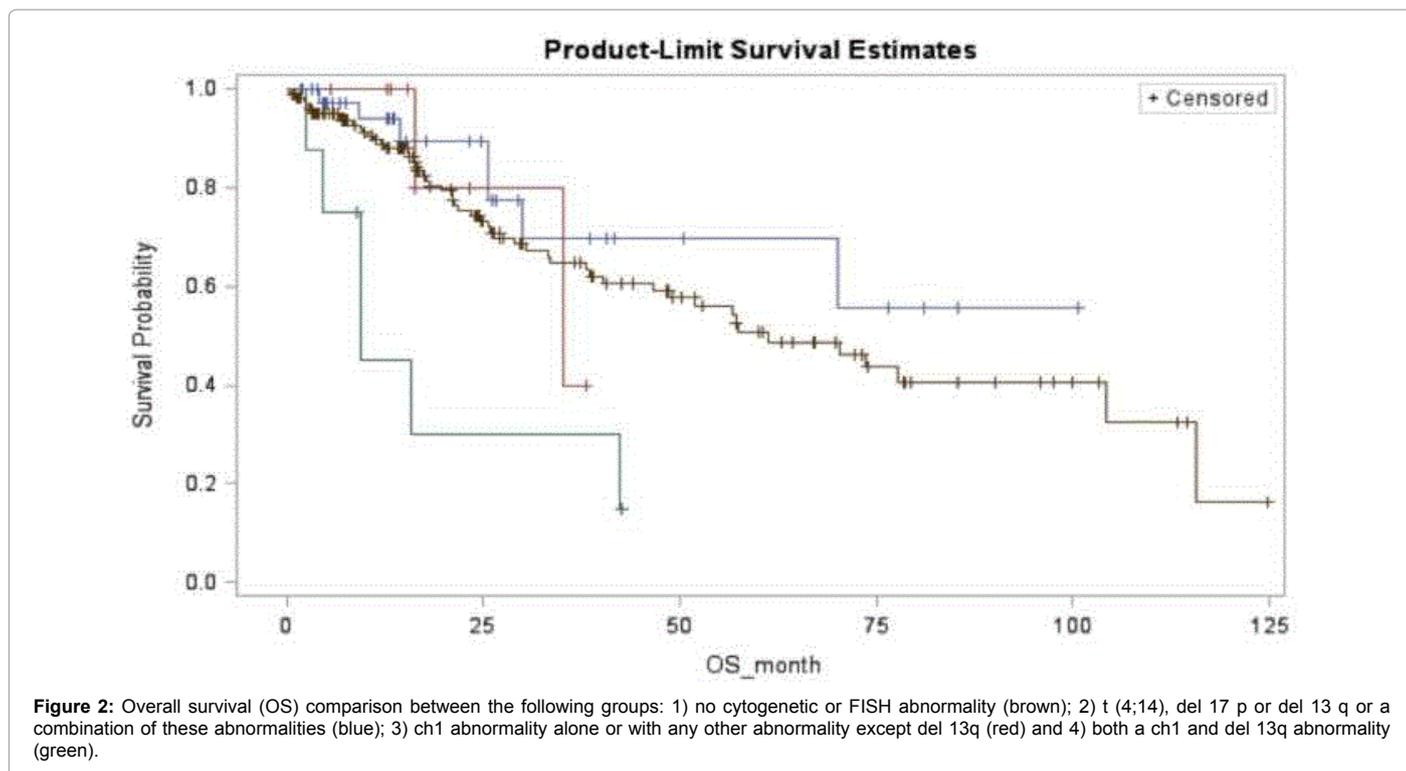
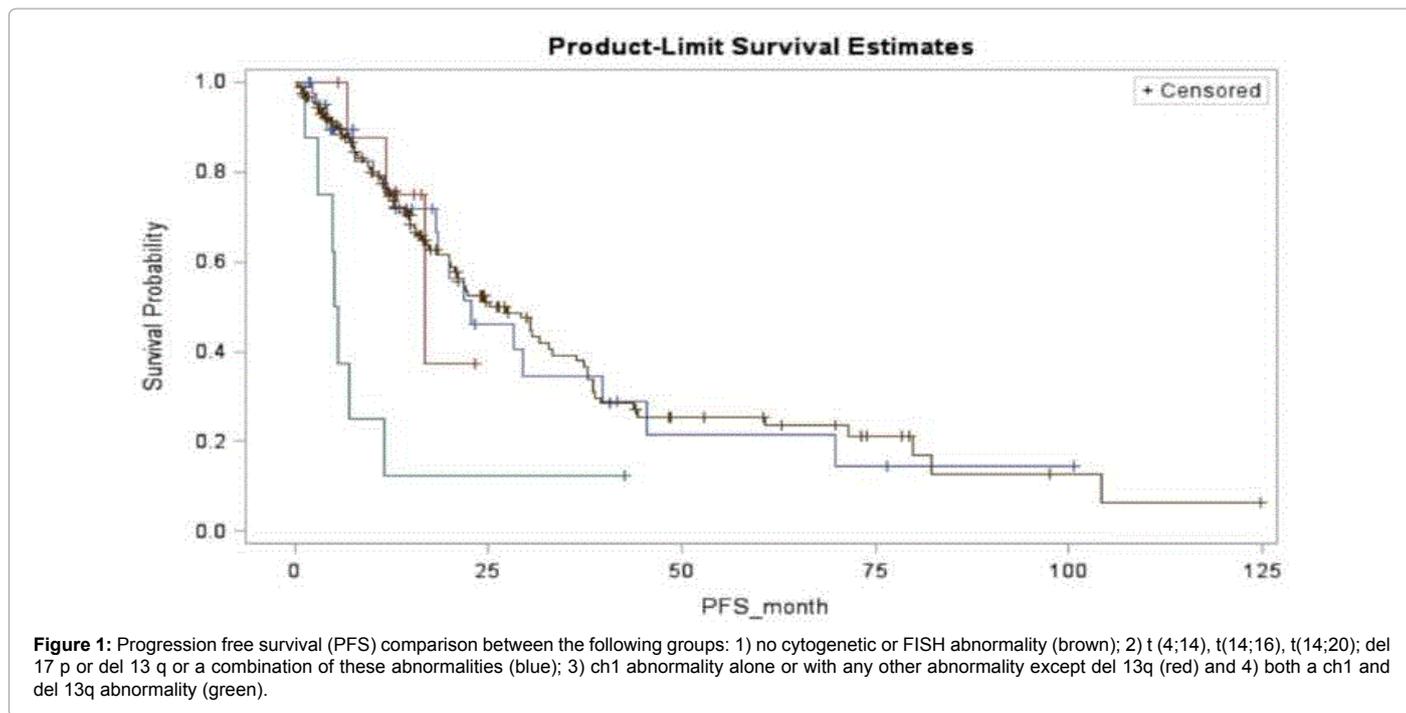
The only covariate that independently predicts lower overall response was achieving less than a PR with 2 consecutive lines of therapy prior to transplant (p = 0.0013, OR = 0.196, 95% CI: 0.072–0.527). Similarly, the only covariate that is independently significantly predicts higher relapse rate was achieving less than a PR with 2 consecutive lines of therapy prior to transplant (p = 0.0391, OR = 5.031, 95% CI: 1.084-23.339). Lacking significant predictors, we did not final

High risk factor	PFS		OS	
	Pr > ChiSq (p value)	Hazard Ratio (95% Hazard Ratio CI limits)	Pr > ChiSq (p value)	Hazard Ratio (95% Hazard Ratio CI limits)
Chromosome 1 abnormality	0.0099	2.652 (1.264- 5.566)	0.0002	4.788(2.098-10.928)
Increased number of prior therapies	0.1852	1.081 (0.963-1.214)	0.0539	1.135 (0.998-1.292)
≤ PR with 2 consecutive lines of therapy	0.0172	2.142 (1.145-4.007)	0.0416	2.148 (1.030-4.481)
Multiple extra medullary plasmacytomas	0.6193	1.232 (0.540-2.810)	0.2503	1.814 (0.657-5.011)
ISS Stage	0.7221		0.47	
ISS stage 2 vs. stage 1	0.6933	0.903 (0.543-1.502)	0.2408	0.674 (0.349-1.303)
ISS stage 3 vs. stage 1	0.4201	0.768 (0.405-1.458)	0.421	0.729 (0.338-1.573)
Salmon - Durie Stage	0.5806		0.996	
Salmon - Durie stage 2 vs. stage 1	0.3001	2.885 (0.389-21.399)	0.9859	*
Salmon - Durie stage 3 vs. stage 1	0.3243	2.706(0.374-19.584)	0.9859	*
Del 13q cyto	0.0608	1.756 (0.975-3.164)	0.216	1.605 (0.759-3.396)
t (4;14)	0.9549	0.978 (0.454-2.105)	0.8969	0.926 (0.289-2.965)
t (14;16)	0.9824	*	0.989	*
del 17p	0.2344	1.741 (0.698-4.342)	0.0727	2.607 (0.916-7.420)
Plasmablastic morphology	0.2824	0.339 (0.047-2.434)	0.9826	*

Table 4: Univariable analysis of high risk factors associated with shorter PFS and OS in subjects that received an auto-HCT for MM. *not computable due to high standard error.

Group	Gene variable	Median PFS in months (95% CI)	Median OS in months (95% CI)
1	No FISH or cytogenetic abnormality (n=154)	24.44 (20.14, 37.88)	57.04 (40.08, 77.80)
2	Del13q;t(4;14); t(14;16); t(14;20) or del 17p (n=38)	26.58 (18.10, 45.47)	69.95(25.53)*
3	Chromosome 1 alone or with any other genetic abnormality EXCEPT del13q (n=8)	16.79 (6.60) *	35.22 (16.30, 35.22)
4	Chromosome 1 and del13q by cytogenetics (n=7)	4.76 (0.98, 7.06)	9.43 (0.99, 15.81)

Table 5: PFS and OS in months for each gene variable group. *The upper bound of 95% CI is not computable. †Median OS has not yet been reached.



any multivariable models worth presenting for both overall response and relapse rate.

Discussion

In this study, we identified that abnormalities of chromosome 1 are significant risk factors associated with the shortest PFS and OS when compared to all other high risk MM groups, including those with other known high risk cytogenetic factors: deletion 17p, t(4;14), t(14;16), t(14;20), deletion 13q (cytogenetic), elevated biomarkers (ISS), high risk clinical extra medullary disease and S-D staging) and morphologic (plasmablastic) features. Our gene risk model demonstrated that subjects with 253 the combination of a chromosome 1 abnormality and cytogenetically detected del 13 q suffered from dismal outcomes (median PFS 4.76 and OS of 9.43 months) post auto-HCT, closely followed by those with chromosome 1 abnormalities alone or in combination with deletion 17p or t(4;14) (median PFS 16.79; OS 35.22 months).

Those with any combination of other well-known high risk FISH or cytogenetic factors: del 13q, del 17p, t(4;14), t(14;16) and t(14;20) had a median PFS of 26.58 months and OS of 35.22 months and those with no abnormalities had median PFS of 24.44 and OS of 57.04 months, both far superior than outcomes for patients with chromosome 1 abnormalities. Finally, despite the heterogeneity and the small number of patients with a chromosome 1 abnormality in this cohort (n= 15) of high risk patients, we have shown using a multivariate model statistical significance of the association of chromosome 1 abnormalities with shortened PFS (HR of 22.93) and OS (HR of 21.218) particularly in those undergoing salvage auto-HCT. We acknowledge that the confidence intervals are very wide given the small number of patients.

The co-existence of gain in 1q with deletion 17p and t(4;14), t(14;16) and t(14;20) and the accumulation of genomic abnormalities over time is recognized as very high risk disease with progressive impact on survival in a recent analysis of 1069 subjects in the MRC IX trial [19]. Interestingly, our data found that del 13q coexisted more commonly with chromosome 1 abnormalities and was significantly more impactful than when combined with other high risk genomic abnormalities. Our data also highlights the complexity of cytogenetic abnormalities in patients with multiple myeloma, and that abnormalities of chromosome 1 are often accompanied by a myriad of other chromosomal alterations that may evolve over time.

The predominance of genes located on chromosome 1 in the high-risk gene expression profile score and the observation that an increase in copy number of 1q21 are associated with relapsed disease 7 raises the question whether aberrations of chromosome 1 are a cause or a consequence of disease progression. Recent evidence shows that the jumping translocation 1q12 is a mechanism for the simultaneous gain of 1q21 and deletion of 17p in cytogenetically defined high-risk disease [20]. Possible biological reasons explaining this observation based upon translational studies are lacking. The cellular and molecular mechanisms of chromosome 1 abnormalities are not well understood but have been proposed to involve decondensation of pericentromeric heterochromatin.1 Chromosomal instability leading to tumor progression through silencing tumor suppressor genes has also been proposed as a mechanism [21].

The only other factor that was independently significantly associated with shortened PFS and OS in the univariable analysis of the entire cohort was achieving less than a PR with 2 consecutive lines of therapy prior to transplant. No particular high risk factor was identified to be independently or jointly associated with PFS or OS

for induction patients. However, for patients receiving salvage HCT, having a chromosome 1 abnormality and a higher Salmon Durie stage (3 vs. 2) are predictive of a shorter PFS and OS. It should be noted that we included MM subjects with any high risk feature that received an auto-HCT as part of their induction and salvage treatment, and thus the outcome measures for the entire cohort are expectedly low due to the exclusion of standard or good risk subjects. In the induction cohort the median PFS and OS are 27.3 and 57.0 months respectively, with 2 and 5 year PFS rates of 65.1% and 53.9% and OS rates of 84.0% and 70.4% respectively, which are somewhat lower to recently published large studies of auto-HCT as consolidation after primary therapy which demonstrate median time to progression of 21-46 months after single autologous transplant, depending on the addition of lenalidomide maintenance [22-24].

These studies (in which patients in the current cohort have participated) have established expected PFS and OS benchmarks for initial auto-HCT that should identify higher risk subsets in the modern era. The median PFS and OS of 18.1 and 30 months in our salvage auto-HCT are comparable to other studies that included all risk groups [25,26]. The past two decades have produced major advances in the treatment of MM, which have led to improvements in response rates and survival for patients with this incurable malignancy. Despite these advances in novel therapies and refinement of stem cell transplant procedures; certain patients still suffer from aggressive disease and succumb to poor outcomes. Efforts to identify particular sub-groups of patients, based on prognostic clinical, biologic and cytogenetic risk factors, which may benefit from particular treatment approaches, are needed. While proteasome inhibitors and immunomodulatory agents have been shown to overcome the poor prognostic impact of certain higher risk genomic abnormalities these therapies have not yet been shown to overcome the poor prognosis of chromosome 1 abnormalities [27]. Given the small number of patients with chromosome 1 abnormalities and the heterogeneity of pre-treatment and maintenance approaches in this cohort, it was not possible to evaluate the impact of specific abnormalities of chromosome 1 or of particular treatments on auto-HCT outcomes.

In summary, we suggest that the presence of a chromosome 1 abnormality, in particular in combination with deletion 13q is a very significant risk factor for short remission duration and overall survival after salvage auto-HCT. Novel induction, transplant, and maintenance approaches need to be considered for this group. Future investigations should be aimed at discovering the true incidence of these abnormalities in large prospective cohorts, the significance of each individual chromosome 1 abnormality (losses, gains, and translocations with various partners) and the impact of particular treatment strategies on overcoming these poor prognostic factors.

Clinical practice points

Controversy exists regarding the impact of various abnormalities of chromosome 1 in multiple myeloma

In this real world cohort of heterogeneously treated patients, chromosome 1 abnormalities significantly impacted PFS and OS in patients undergoing salvage auto-HCT

Future studies are needed to further characterize different chromosome 1 abnormalities and their impact on treatment outcomes.

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