Leukemia Research 76 (2019) 58–64

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Clinical impact of chromothriptic complex chromosomal rearrangements in newly diagnosed multiple myeloma

Gurvinder Kaur[a], Ritu Gupta[a,*], Nitin Mathur[a], Lata Rani[a], Lalit Kumar[b], Atul Sharma[b], Vishwajeet Singh[c], Anubha Gupta[d], Om Dutt Sharma[a]

[a] Laboratory Oncology Unit, Dr. B.R.A.IRCH, All India Institute of Medical Sciences (AIIMS), New Delhi, India
[b] Department of Medical Oncology, Dr. B.R.A.IRCH, AIIMS, New Delhi, India
[c] Department of Biostatistics, AIIMS, New Delhi, India
[d] Department of Electronics & Communications, Indraprastha Institute of Information Technology (IIIT), New Delhi, India

ARTICLE INFO

Keywords:
Array CGH
Chromosomal rearrangements
Chromothripsis
CTLPscanner
Multiple myeloma

ABSTRACT

Complex Chromosomal Rearrangements (CCRs) are increasingly being reported as genetic risk factors of clinical significance in cancer owing to their identification using high resolution whole genome profiling technologies. This study employed high resolution CGH + SNP microarrays for whole genome copy number variations (CNV) profiling and identified CCRs in 11/107(10%) newly diagnosed Multiple Myeloma (MM) patients. Six patients exhibited Chromothripsis (CTH) among seven chromosomes that were confirmed with automated CTLPscanner web tool and; five cases displayed chromoplexy (CPL) which involved multiple chromosomes. Presence of chromothripsis in chromosome 17 in three out of six patients indicate a link between TP53 aberrations and incidence of CTH. Multivariable Cox regression model demonstrated a significant association of CTH with poor PFS (HR = 3.09, p = 0.010) and OS (HR = 3.31, p = 0.024) which suggests that CTH is an additional independent prognostic marker in multiple myeloma. Addition of CTH in risk stratification models in clinical setting in multiple myeloma may help in upfront identification of high risk patients for suitable customized therapy.

1. Introduction

Multiple Myeloma (MM) is a hematopoietic malignancy of plasma cells characterized by complex and heterogeneous genome with multiple copy number variations and chromosomal lesions such as translocations, insertions and deletions [1]. Specific gene fusions following translocations and dysregulated gene expression signatures have been shown to affect prognosis and thus have been integrated in the risk stratification schema of myeloma patients [2]. Approximately 40% of myeloma patients exhibit translocations in the immunoglobulin heavy chain (*IGH*) locus that bring oncogenes in close proximity of *IGH* enhancer elements leading to their upregulation and activation. Specific translocations [t(14;16) with *c-MAF* and t(14;20) with *MAFB]*, del17p13 (*TP53*) and non hyperdiploid status are considered to be associated with adverse prognosis in multiple myeloma [3].

Recent advent of genome wide screening techniques such as comparative genomic hybridization SNP microarrays (aCGH + SNP) and next generation sequencing (NGS) have allowed high resolution mapping of genome-wide copy number aberrations and enhanced our ability to detect complex chromosomal rearrangements (CCRs) [4,5]. Distinct molecular mechanisms and features of three types of complex chromosomal rearrangements i.e., Chromothripsis (CTH), Chromoanasynthesis and Chromoplexy have already been established and reviewed extensively [6]. These phenomena have been shown to be associated with solid tumors as well as haematological malignancies. Among the CCRs, CTH has been reported frequently in a wide variety of tumors, usually at a frequency of ~2% to 3% [7–9]. Exceptionally, in certain tumors, the frequency of CTH can be as high as 25% e.g., in osteosarcoma and chordomas [7–9].

In MM, the incidence of CTH is around 1% [10]. A recent NGS based study reported CTH in seven out of nine MM cell lines [11]. CTH pattern was most frequently observed in chr 1 in 5/7 cell lines, followed by chr 11 and 12 in 3/7 cell lines [11].Occurrence of CTH has also been reported to affect chromosomes 2, 3, 8q, 10, 16q and 18in MM [10,12]. Another recent study identified CTH on chromosomes 1 and 16 and additional complex step-wise genomic events across multiple chromosomes 1, 3, 4, 8, 10, 14, 16, 17, 20 and 22 in patients with MM [13].Thus, the relative differences in CTH patterns observed in

* Corresponding author at: R. No.239, Second Floor, Laboratory Oncology Unit, Dr. B.R.A.IRCH, AIIMS, Ansari Nagar, New Delhi 110029, India.
E-mail addresses: drritugupta@gmail.com, drritu.laboncology@aiims.edu (R. Gupta).

https://doi.org/10.1016/j.leukres.2018.12.005
Received 1 October 2018; Received in revised form 12 December 2018; Accepted 14 December 2018
Available online 15 December 2018

Table 1
Profile of Chromothriptic (CTH) chromosomal rearrangements and clinical outcome in multiple myeloma patients (n = 6).

Case ID (Age/ Sex/ ISS)	CTH Region Win size (Mb)	CTH Chr: Cytoband	CTH position Start – Stop	CNA status change times (≥10) (Switch number)	No of gains + losses + LOH = total events	Likeli-hood ratio log10 (≥8)	Treatment	First response	PFS (Months)	OS (Months)	Clinical outcome
SM87 (69/F/ 3)	102.53	Chr 1: 1q21.1-1q44	145000001-247531392	26	10 + 12 + 5 = 27	29.63	VD	PD	24.53	43.87	Alive, in CR
SM167 (67/ M) [ISS 3]	243.2	Chr 2: 2p25.3-2q37.3	1- 243199373	21	10 + 7 + 5 = 22	27	VRD	PD	9.97	10.83	Death
SM125 (47/F) [ISS 3]	102.53	Chr 4: 4p12-4q31.22	45000001-147531392	21	4 + 12 + 6= 22	21.11	RD	PD	8	8	Death
	30	Chr 17: 17p13.3-17q11.2	1- 30000000	15	9 + 6+ 1 = 16	11					
SM91 (60/F) [ISS 3]	78.08	Chr 17: 17p13.3-17q25.3	3117962 -81195210	19	12 + 5 + 3 = 20	17	VRD	PD	46	4.67	Death
SM111 (50 /F) [ISS 3]	90.35	Chr 1: 1p36.33-1q22.2	1- 90354753	12	1 + 11 + 2= 14	8	VD	PD	10.67	10.7	Death
SM114 (51/F) [ISS 2]	40	Chr 17: 17p13.1-17q21.33	10000001 - 50000000	12	4 + 8+ 2 = 14	8	VRD	PD	5.83	5.83	Death

Abbreviations: CTHChromothripsis; CNA ; copy number alterations; ISSInternational Staging system; VRDBortezomib + Lenalidomide + Dexamethasone; PFSProgression free survival; PDProgressive disease; OSOverall survival; CRComplete remission.

available studies suggest a need to carry out further studies to elucidate additional CTH patterns in multiple myeloma. CTH has also been shown to be associated with aggressive subtypes and poor survival in AML [14,15], ALL [16] and CLL [17]. Only a limited number of studies have indicated association of CTH with progression free survival and overall survival in MM [10,12,13]. A recent study demonstrated correlation of CTH with resistance to Bortezomib therapy in MM cell lines as well as patients [11].

With the available data, it is thus plausible that abrupt emergence of CCRs during tumorigenesis leads to a rapid genomic chaos, confers selective advantage to malignant cells and maneuvers their response to therapy as well as aggressive clonal propagation. The present study was undertaken to examine CCRs in myeloma genomes using high resolution CGH + SNP microarrays and analyze their clinical impact in myeloma genomes.

2. Materials and methods

2.1. Patients

Treatment naïve multiple myeloma patients (n = 107) diagnosed at our center as per IMWG guidelines and treated with novel agents and for whom the clinical and experimental data was available were evaluated [18]. The study was approved by the local institution ethical committee and study subjects were enrolled following their voluntary written informed consent. The clinical and laboratory details for the enrolled patients were obtained from the medical records.

2.2. Microarray analysis

Plasma cells (CD138 +) were purified from bone marrow aspirates using magnetic microbeads as per manufacturer's recommendations (Miltenyi Biotec, Germany). Genomic DNA was isolated from CD138 + enriched plasma cells with QIAamp DNA Blood Minikit (Qiagen, Germany). The DNA quantity and quality were examined using absorbance at 260/280 obtained with Nanodrop spectrophotometer. SurePrint G3 Cancer CGH + SNP microarray (G5922 A, Design ID 030587, Format 4 x 180 K with 110712 CGH and 59647 SNP features) with an overall median probe space of 25 kb, (i.e. 1 probe/0.5-1 KB) was used for profiling MM whole genomes at high resolution as per the manufacturer's instructions (Agilent Technologies, Santa Clara, USA). Relative differences in signal intensities between the test sample and Agilent sex matched CNV reference were expressed as a log2 ratio for each marker and corresponding copy number values were determined. Genotype information for the CNVs and the SNP frequencies of uncut alleles were analyzed with Cytogenomics software version 4.0.3.12 (Agilent Technologies, Santa Clara, USA).Genome assembly UCSC hg19 (NCBI build 37, February 2009) was used for all reference genome annotations. Tracks of gains and losses originating from Agilent's sex matched reference DNA were excluded at the time of analysis. Aberration calls were identified using mosaic aberration detection filter with ≥ 5 consecutive probes and exceeding ≥ 0.15 average log2 absolute log ratio.

2.3. Detection of complex chromosomal rearrangements (CCRs)

Complex chromosomal rearrangements were assessed in CGH + SNP arrays based on number of segmental rearrangements and copy number states [4–6] that were visualized in Cytogenomics 4.0.3.12. The CTH patterns were characterized by involvement of one to five chromosomes and multiple breakpoints mostly clustered with ≥ 10 changes per chromosome. Whereas, the CPL patterns were characterized by involvement of > 6 chromosomes with fewer but randomly distributed breakpoints. The CTH cases identified with cytogenomics were further verified by automated 'CTLP scanner' package (http://cgma.scu.edu.cn/CTLPScanner/) [19]. The analysis parameters

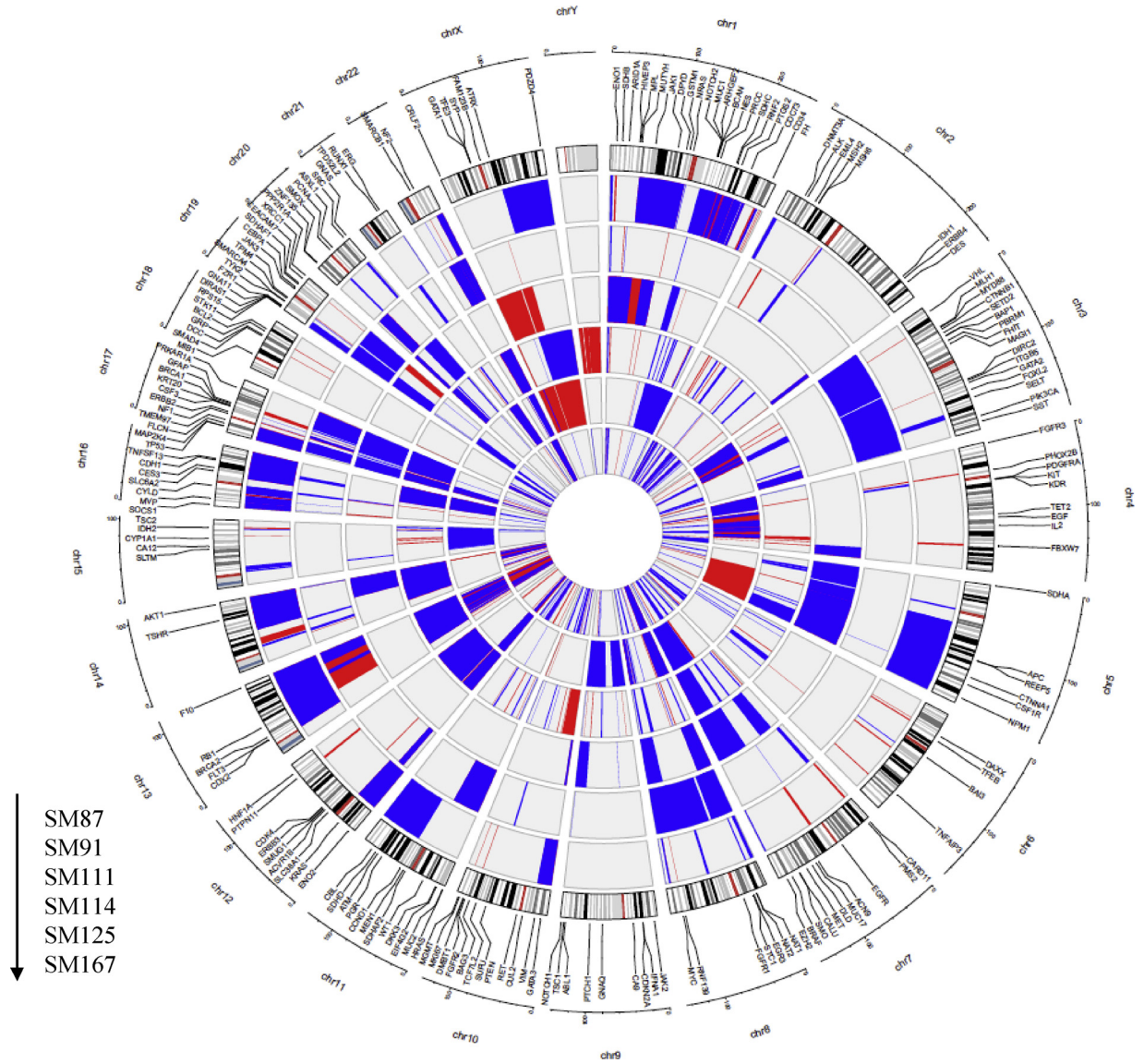

Fig. 1. Circos plot of chromothriptic chromosomes in multiple myeloma patients (n = 6) drawn with shinyCircos. The outermost track depicts chromosomal ideogram followed by inner track of gene labels including oncogenes, tumor suppressor genes and fusion genes obtained from COSMIC cancer census. Deletions and gains are shown in red and blue color respectively. The outermost track depicts SM87 followed by SM91, SM111, SM114, SM125 and SM167 respectively in inward direction (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

that were used for 'CTLP scanner' included signal distance between adjacent segments of 0.3 and minimum segment size of 10 kb A threshold value of ≥10 was used to define switch or copy number status change times for CTH while the log10 likelihood ratios was kept constant at a default value of ≥8. The Circos plots were generated with the help of R/Shiny application 'shinyCircos' (www.shinycircos.ncpgr.cn) [20]. A list of annotated genes lying in the chromothriptic region and known to be oncogenes/ fusion genes/ tumor suppressor genes was obtained from cancer gene census list of Feb 2018 downloaded from COSMIC (https://cancer.sanger.ac.uk/census). The cytoband.txt file was downloaded from UCSC (http://hgdownload.cse.ucsc.edu/goldenPath/hg19/database/) and used for preparing the circos ideogram.

2.4. Survival analysis

Overall survival (OS) was defined as the time from the date of diagnosis to date of death or last followup. Progression free survival (PFS) was estimated as duration from start of treatment to disease progression or death. The PFS and OS were compared between groups using Kaplan-Meier survival analysis followed by log-rank test. Hazard ratio (HR) for PFS and OS was calculated using Cox proportional hazard regression (STATA/SE software ver 14.2, Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Clinical parameters

The clinical and laboratory parameters, therapy received and response to therapy of all the patients (n = 107) evaluated in this study are given in Supplementary Table 1. The median age of the patient cohort was 58 years (range: 30–82 years); 31(28.7%) patients were > 65 years of age. In this study, 10 (9.3%) patients were in ISS 1, 25 (23.4%) in ISS 2 and 72 (67.3%) in ISS 3. Renal impairment (serum creatinine ≥ 2 mg/dl and/or estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2) was observed in 22 (20.6%) patients. All the patients received novel agents as primary therapy; 57% patients received doublet therapy with either thalidomide or lenalidomide or

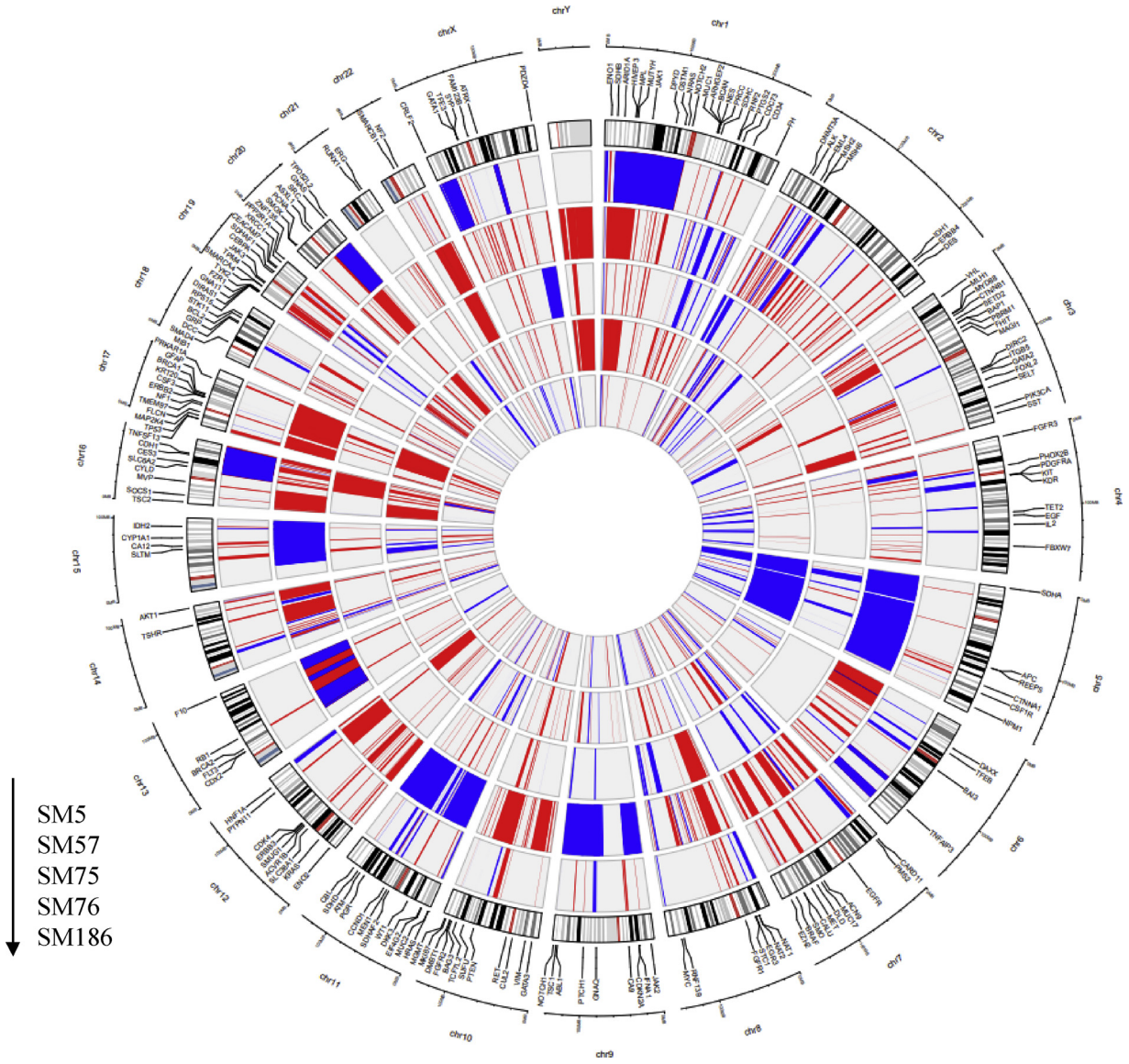

Fig. 2. Circos plot for multiple Chromoplexic chromosomes observed in myeloma patients (n = 5) drawn with shinyCircos. The outermost track depicts chromosomal ideogram followed by inner track of gene labels including oncogenes, tumor suppressor genes and fusion genes obtained from COSMIC cancer census. Deletions and gains are shown in red and blue color respectively. The outermost track depicts SM5 followed by SM57, SM75, SM76 and SM186 respectively in inward direction (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

bortezomib and 43% received triplet regimen. With a median follow up period of 25 months, 71 patients progressed and 43 died; the median PFS was 24 months and the median OS was 29 months. An overall treatment response including complete remission (CR), very good partial remission (VGPR), and partial remission (PR) was achieved in 67.6% patients.

3.2. Characteristics of complex chromosomal rearrangements (CCRs) in multiple myeloma patients

Genome wide structural variation profiling examined through aCGH + SNP based analysis in 107 newly diagnosed MM patients revealed presence of CCRs among 11 (10%) patients. Of these, six patients (5.5%) exhibited CTH (Table 1; Supplementary Fig. 1). The CTH pattern was spread across chromosomes viz. chr 1 (in two cases SM87 and SM111), chr 2 (in SM167), chr 4 (in SM125) and chr 17 (in three case in SM125, SM91, SM114). CTH was distributed across whole chromosomes except one case (SM87) where it was concentrated exclusively in chr1q arm (Table 1). The size of chromothriptic genome region varied from 30 Mb (in SM125 chr 17: 17p13.3-q11.2) to 243 Mb (in SM167 chr2:2p25.3-2q37.3). Multiple events of gains and losses were recorded as shown in Table 1 and Supplementary Fig. 1 and the copy number alterations (CNA) status (or switch number) changed ≥10 times ranging from 12 to 26 times per CTH chromosome. A circos plot was drawn showing CTH chromosomes for all the six cases (Fig. 1). The outer most ring of circos plot depicts various genes involved in cancer (oncogenes/ fusion/ tumor suppressor genes; source COSMIC census) that may be implicated to be mechanistically involved in development and/or progression of the disease in these patients.

Of all the chromosomes, CTH was most frequently observed in chromosome number 17 (among three out of 6 cases). The CTH region spanned from 17p13.1 to a maximum upto 17q25.3 and the size ranged from 40 Mb to 78 Mb (Table 1; Supplementary Fig. 1). The switch numbers corresponding to changes in CNA status were between 12 to 19 with frequent events of gains and losses. The gene *TP53* located on 17p13.1 was found to be deleted in two cases SM125 and SM114 (mean log ratio -0.57; Supplementary Fig. 1).

Another category of CCRs i.e. Chromoplexy was observed in five

Table 2
Univariate and multivariate analysis for Overall survival (OS) and Progression free survival (PFS) in MM patients (n = 107).

S No	Parameter		Overall Survival (OS)					Progression free survival (PFS)				
			OS (Months)	Univariate		Multivariate		PFS (Months)	Univariate		Multivariate	
				HR (p value)	95% CI	HR (p value)	95% CI		HR (p value)	95% CI	HR (p value)	95% CI
1	CTH	Negative (n = 101)	NR	3.67 **(0.007)**	1.42- 9.49	3.31 **(0.024)**	1.17- 9.33	24.8	3.09 **(0.010)**	1.31- 7.29	2.52 **(0.037)**	1.05-6.05
		Positive (n = 06)	8					8.0				
2	CPL	Negative (n = 102)	42.5					23.0	0.15 (0.061)	0.02-1.09	–	–
		Positive (n = 5)	NR					NR				
3	Response	0 (n = 51)	NR	4.51(< **0.001**)	2.25- 9.03	3.92 **(0.001)**	1.77-8.70	34.4	3.2 (< **0.001**)	2.00-5.40	3.04 (< **0.001**)	1.84-5.02
		1 (n = 54)	20.9					10.2				
4	Hemoglobin	< 9.2 (n = 53)	42.5	0.86 (0.638)	0.47-1.57	–	–	20.9	0.72 (0.189)	0.45-1.16	–	–
		≥9.2 (n = 53)	NR					27.4				
5	Creatinine	< 2 (n = 82)	42.5	1.05 (0.87)	0.51-2.15	–	–	24.6	1.27 (0.37)	0.74-2.18	–	–
		≥2 (n = 25)	NR					23.1				
6	β2 M	< 5.5 (n = 35)	NR	1.02 (0.93)	0.54-1.94	–	–	29.6	1.47 (0.151)	0.86-2.49	–	–
		≥5.5 (n = 72)	NR					21.0				
7	Albumin	< 3.5 (n = 42)	NR	1.01 (0.968)	0.54- 1.86	–	–	20.9	0.85 (0.52)	0.53-1.38	–	–
		≥3.5 (n = 63)	37.9					24.2				
8	Chemotherapy regimen	Doublet (n = 62)	37.9	0.68 (0.25)	0.35- 1.31	–	–	24.2	0.98 (0.96)	0.60-1.60	–	–
		Triplet (n = 44)	NR					23.5				
9	Del 1p	Negative (n = 76)	37.9	0.73 (0.37)	0.36-1.46	–	–	24.4	0.81 (0.45)	0.48-1.38	–	–
		Positive (n = 31)	NR					24.5				
10	Amp 1q	Negative (n = 50)	NR	1.28 (0.41)	0.70- 2.36	–	–	25.0	1.08 (0.74)	0.67-1.73	–	–
		Positive (n = 57)	42.5					21.0				
11	Del 12p	Negative (n = 89)	NR	1.54 (0.23)	0.75- 3.12	–	–	26.9	0.67 (0.084)	0.93-2.94	–	–
		Positive (n = 18)	20.9					11.5				
12	Del 13q	Negative (n = 57)	NR	3.60 (< **0.001**)	1.84 -7.03	2.36 (0.052)	0.99- 4.27	32.9	2.05 **(0.003)**	1.27-3.30	1.68 **(0.036)**	1.03-2.73
		Positive (n = 50)	28.3					13.5				
13	Del 14q	Negative (n = 73)	37.9	0 .84 (0.61)	0.44-1.62	–	–	24.4	0.93 (0.804)	0.56-1.56	–	–
		Positive (n = 34)	NR					24.7				
14	Del 16q	Negative (n = 81	NR	1.24 (0.52)	0.64 -2.4	–	–	24.4	0.85 (0.56)	0.49-1.47	–	–
		Positive (n = 26)	37.9					24.5				
15	Del 17p	Negative (n = 93)	42.5	1.53 (0.28)	0.70- 3.33	–	–	24.46	0.96 (0.920)	0.47-1.94	–	–
		Positive (n = 14)	35.4					24.53				
16	ISS stage	II (n = 25)	37.7	0.74 (0.58)	0.25-2.14	–	–	32.9	1.26 (0.64)	0.45-3.49	–	–
		III (n = 72)		0.64 (0.36)	0.24-1.66	–	–	21	1.60 (0.31)	0.63-4.02	–	–

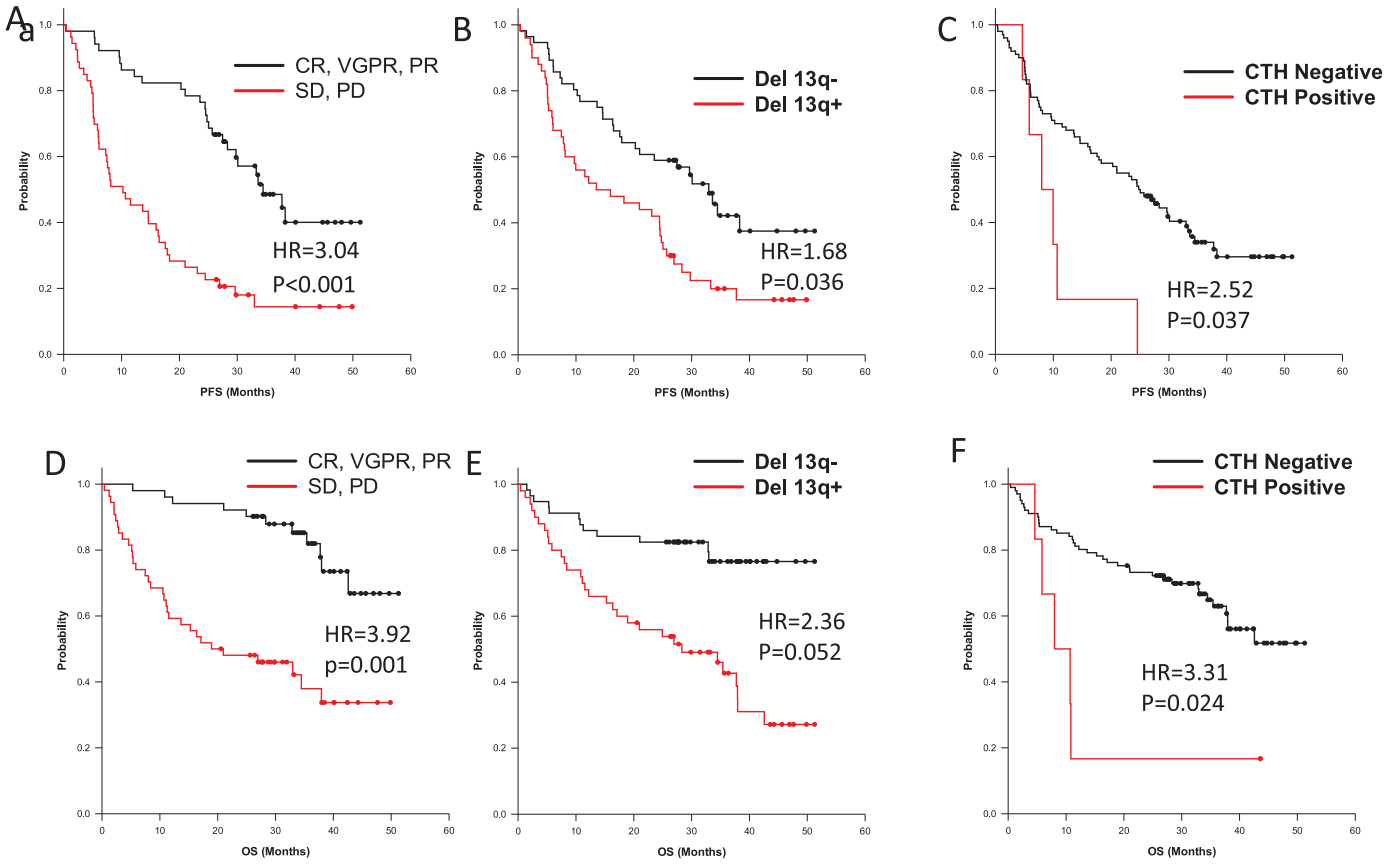

Fig. 3. Kaplan Meier survival curves for progression free survival in multiple myeloma patients stratified on the basis of(A) response, (B) Del(13q) and (C) Chromothripsis (CTH), and; overall survival in multiple myeloma patients stratified on the basis of (D) response, (E) Del(13q) and (F) CTH.

cases (SM5, SM57, SM75, SM76 and SM186). The CPL regions appeared in a totally shattered state and were scattered across whole genome across multiple number (> 6) chromosomes (Fig. 2). The number of CNA status changes among CPL chromosomes varied beyond 5 (at a likelihood log10 ratio of ≥8) and the oscillating patterns of gains or normal regions or deletions as well as the complexity of genes located at CPL regions across various chromosomes are depicted in circos plot (Fig. 2).

3.3. Clinical correlation of CCRs with progression free and overall survival

The clinical status of Myeloma patients with CTH at the time of first response to therapy and last follow up was evaluated. Five out of six patients with CTH died within short duration of 10.8 months. The only exception is SM87 who despite having 102.5 Mb CTH region corresponding to 1q21.1 to 1q44 chromosomal region responded well to bortezomib-dexamethasone therapy and continues to be in complete remission (Table 2).

To assess the prognostic association of CCRs, a univariate and multivariate analysis was carried out for CCRs (CTH and CPL) as well as other prognostic parameters associated with survival such as ISS stage, deletions (1p, 12p, 14q, 16q, 17p), amp1q, response to therapy, levels of creatinine, hemoglobin and β2 Microglobulin (Table 2). In univariate analysis, CTH (PFS: HR = 3.09, 95%CI = 1.31–7.29, p = 0.010; OS:HR = 3.67, 95%CI = 1.42–9.49, p = 0.007), response (PFS: HR = 3.28, 95%CI = 2.0–5.4, p= < 0.001; OS: HR = 4.51, 95%CI = 2.25–9.03, p= < 0.001) and del 13q (PFS: HR = 2.05, 95%CI = 1.27–3.30, p = 0.003; OS: HR = 3.60, 95%CI = 1.84–7.03, p= < 0.001) were significantly associated with PFS and OS both. In multivariate analysis, CTH (HR = 2.5, 95%CI = 1.05–6.05, p = 0.037), response (HR = 3.04, 95%CI = 1.84–5.02, p < 0.001) and del 13q (HR = 1.68, 95%CI = 1.03–2.73, p = 0.036) were statistically independent predictors of PFS whilst only CTH (HR = 3.3, 95%CI = 1.17–9.31, p = 0.024) and response (HR = 3.9, 95%CI = 1.77–8.70, p < 0.001) retained significant independent prognostic impact for OS (Fig. 3).

4. Discussion

Multiple Myeloma is a plasma cell proliferative disorder that instigates as a benign premalignant MGUS followed by gradual evolution to SMM, MM or Plasma cell leukemia [21]. This hierarchical mode of evolution of myeloma is supported by clonal expansion of cells that can acquire genetic lesions over time. Since incidence of CTH has been demonstrated in myeloma genomes, it is possible that a simultaneous discontinuous evolutionary pathway may also be operational at least in part and may be in mosaic or sub clonal level that may augment disease progression or relapse in those patients. This bimodal prototype of continuous cum discontinuous mode of myeloma progression, therefore, explains why some of the patients carrying high risk genetic signatures including CTH might bypass and succumb more rapidly to progression or relapse.

In MM, deletion of tumor suppressor gene *TP53* on chromosome region 17p13 is a key biomarker of poor prognosis Recently, it has been reported that *TP53* regulates G2/M phase checkpoint and prevents chromosome shattering [22,23]. Incidentally, deletion or dysregulation of *TP53* function during tumor development has been implied in likelihood of chromothriptic chromosomal fragmentation among AML, pancreatic cancer and pediatric medulloblastoma [4,9]. It appears that a parallel analogy might exist in context of MM since loss of *TP53* is strongly implicated in tumor development and attributes high risk. A relatively higher incidence of CTH in chromosome 17 observed in this

study and also reported by Sawyer et al. [22] seems to be in agreement with this notion but large scale high resolution whole genome deep sequencing studies are required to confirm this observation [12].

In this study, all the newly diagnosed treatment naïve cases of MM harboring CTH except one succumbed to death with a median OS of 8 months. A recent study on patients with multiple myeloma and MGUS reported 17 CCR events among 9 cases; of which six relapsed while one died. An earlier large scale study (n = 764) on newly diagnosed MM patients identified CTH in 10 (1.3%) patients of whom 5 relapsed within 10 months of diagnosis and 4 among these died. [10] A recent case report also demonstrated rapid extramedullary relapse and death within 23 months of a patient harboring CTH in chromosome 18 [12]. Lee et al recently demonstrated demonstrated increased frequencies of CCRs among Bortezomib resistant MM subgroup suggesting correlation of CTH with response to therapy [11]. Hence, our observations on CCRs in MM in this study are in agreement with the suggestion that occurrence of CCRs correlates with adverse clinical outcome. -Hence, CTH can have a profound effect and its inclusion in routine genome diagnostics and genetic risk stratification can aid in identification of high risk patients.

5. Conclusion

Based on above, CCRs such as CTH trigger faster progression in MM with poor overall survival, although underlying mechanisms of CCR related molecular events in fomenting plasma cell transformation and speeding up progression remain unresolved. Further NGS based studies could help read junctional complexities of rearranged genomic segments and unravel the underlying potential mechanisms. It is therefore suggested that CCRs being associated with poor outcomes, need to be investigated further for possible consideration as one of the factors that could influence therapy decisions and reclassification of individual risk stratification in MM.

Author contributions

RG designed, coordinated the study, performed analysis, interpretation and wrote the manuscript. GK performed analysis, interpretation and wrote the manuscript. NM and LR performed the experiments and contributed in manuscript writing. LK, AS and AG analyzed the data and contributed in manuscript writing. Statistical analysis was performed by VS. ODS provided laboratory assistance.

Funding

This work was supported by the Department of Biotechnology, Ministry of Science & Technology, GOI (BT/ PR/7136/MED/30/901/2012 and BT/MED/30/SP11006/2015) & All India Institute of Medical Sciences, New Delhi (A411/RS).

Acknowledgements

We gratefully acknowledge the assistance provided by Miss Isha Saini in drawing circos plots.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2018.12.005.

References

[1] N.S. Joseph, S. Gentili, J.L. Kaufman, S. Lonial, A.K. Nooka, High-risk multiple myeloma: definition and management, Clin. Lymphoma. Myeloma Leuk. 17S (2017) S80–S87.
[2] M.F. Kaiser, B.A. Walker, S.L. Hockley, D.B. Begum, C.P. Wardell, D. Gonzalez, F.M. Ross, F.E. Davies, G.J. Morgan, A TC classification-based predictor for multiple myeloma using multiplexed real-time quantitative PCR, Leukemia 27 (2013) 1754–1757.
[3] S.V. Rajkumar, Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management, Am. J. Hematol. 91 (2016) 719–34.4M.
[4] M. Poot, Of simple and complex genome rearrangements, chromothripsis, chromoanasynthesis, and chromosome chaos, Mol. Syndromol. 8 (2017) 115–117.
[5] A.J. Holland, D.W. Cleveland, Chromoanagenesis and cancer: mechanisms and consequences of localized, complex chromosomal rearrangements, Nat. Med. 18 (2012) 1630–1638.
[6] R.L. Collins, H. Brand, C.E. Redin, C. Hanscom, C. Antolik, M.R. Stone, J.T. Glessner, T. Mason, G. Pregno, N. Dorrani, et al., Defining the diverse spectrum of inversions, complex structural variation, and chromothripsis in the morbid human genome, Genome Biol. 18 (2017) 36.
[7] P.J. Stephens, C.D. Greenman, B. Fu, F. Yang, G.R. Bignell, L.J. Mudie, E.D. Pleasance, K.W. Lau, D. Beare, L.A. Stebbings, et al., Massive genomic rearrangement acquired in a single catastrophic event during cancer development, Cell 144 (2011) 27–40.
[8] M.J.K. Jones, P.V. Jallepalli, Chromothripsis: chromosomes in crisis, Dev. Cell 23 (2012) 908–917.
[9] T. Rausch, D.T.W. Jones, M. Zapatka, A.M. Stütz, T. Zichner, J. Weischenfeldt, N. Jäger, M. Remke, D. Shih, P.A. Northcott, et al., Genome sequencing of pediatric medulloblastoma links catastrophic DNA rearrangements with TP53 mutations, Cell 148 (2012) 59–71.
[10] F. Magrangeas, H. Avet-Loiseau, N.C. Munshi, S. Minvielle, Chromothripsis identifies a rare and aggressive entity among newly diagnosed multiple myeloma patients, Blood 118 (2011) 675–678.
[11] K.J. Lee, K.H. Lee, K.-A. Yoon, J.Y. Sohn, E. Lee, H. Lee, H.-S. Eom, S.-Y. Kong, Chromothripsis in treatment resistance in multiple myeloma, Genomics Inform. 15 (2017) 87–97.
[12] J. Smetana, J. Oppelt, M. Štork, L. Pour, P. Kuglík, Chromothripsis 18 in multiple myeloma patient with rapid extramedullary relapse, Mol. Cytogenet. 11 (7) (2018).
[13] N.K. Berry, A. Dixon-McIver, R.J. Scott, P. Rowlings, A.K. Enjeti, Detection of complex genomic signatures associated with risk in plasma cell disorders, Cancer Genet. 218–219 (2017) 1–9.
[14] F.G. Rucker, A. Dolnik, T.J. Blatte, V. Teleanu, A. Ernst, F. Thol, et al., Chromothripsis is linked to TP53 alteration, cell cycle impairment, and dismal outcome in acute myeloid leukemia with complex karyotype, Haematologica 103 (2018) e17–e20.
[15] T. Bochtler, M. Granzow, F. Stölzel, C. Kunz, B. Mohr, M. Kartal-Kaess, et al., Marker chromosomes can arise from chromothripsis and predict adverse prognosis in acute myeloid leukemia, Blood 129 (2017) 1333–1342.
[16] M. Forero-Castro, C. Robledo, R. Benito, M. Abaigar, A. Africa Martin, M. Arefi, et al., Genome-wide DNA copy number analysis of acute lymphoblastic leukemia identifies new genetic markers associated with clinical outcome, PLoS One 11 (2016) e0148972.
[17] I. Salaverria, D. Martin-Garcia, C. Lopez, G. Clot, M. Garcia-Aragones, A. Navarro, et al., Detection of chromothripsis-like patterns with a custom array platform for chronic lymphocytic leukemia, Genes Chromosomes Cancer 54 (2015) 668–680.
[18] S.V. Rajkumar, M.A. Dimopoulos, A. Palumbo, J. Blade, G. Merlini, M.V. Mateos, S. Kumar, J. Hillengass, E. Kastritis, P. Richardson, O. Landgren, B. Paiva, A. Dispenzieri, et al., International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, Lancet Oncol. 15 (2014) e538–48.
[19] J. Yang, B. Liu, H. Cai, Chromothripsis detection and characterization using the CTLPScanner Web Server, Methods Mol. Biol. 1769 (2018) 265–278.
[20] Y. Yu, Y. Ouyang, W. Yao, shinyCircos: an R/Shiny application for interactive creation of Circos plot, Bioinformatics 34 (2018) 1229–1231.
[21] S. Manier, K.Z. Salem, J. Park, D.A. Landau, G. Getz, I.M. Ghobrial, Genomic complexity of multiple myeloma and its clinical implications, Nat. Rev. Clin. Oncol. 14 (2017) 100–113.
[22] J.R. Sawyer, E. Tian, C.J. Heuck, J. Epstein, D.J. Johann, C.M. Swanson, J.L. Lukacs, M. Johnson, R. Binz, A. Boast, et al., Jumping translocations of 1q12 in multiple myeloma: a novel mechanism for deletion of 17p in cytogenetically defined high-risk disease, Blood 123 (2014) 2504–2512.
[23] M. Poot Genes, Proteins, and biological pathways preventing chromothripsis, Methods Mol. Biol. 1769 (2018) 231–251.