Plasma Cell Dyscrasias in India-2017 Updates

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Abstract Rapid advances are being made in the field of plasma cell dyscrasias. Many abstracts pertaining to the laboratory aspects, clinical features, treatment modalities and outcome of plasma cell dyscrasias were presented at Hematocon 2017. All the total of 24 abstracts pertaining to plasma cell dyscrasias presented at the Hematocon 2017 were reviewed. Out of them 10 were original research and 14 were case reports/short case series. The key findings of original research studies conducted in India are being summarized. Exciting research in the field of plasma cell dyscrasias is being carried out by various centers in the country. Data presented on various aspects of research in plasma cell disorders is encouraging. Multicentric research in the field plasma cell dyscrasias should be encouraged to highlight the various aspects of disease biology and challenges in management unique to our country.

Keywords Plasma cell disorders · Multiple myeloma · India

Introduction

The last decade has witnessed tremendous strides in our understanding of plasma cell dyscrasias and the therapy of these disorders. Like the previous years, Hematocon held at Guwahati this year (Hematocon 2017), provided an excellent platform to discuss and present the contemporary

research on various aspects of hematology including plasma cell disorders from the country and abroad.

Methods

A total of 24 abstracts pertaining to plasma cell disorders presented at the conference were reviewed. Out of 24 abstracts, 10 were original research and 14 were case reports/short case series. The key findings of the original research abstracts on diagnosis, risk stratification, clinical profile and treatment aspects of plasma cell disorders presented at the Hematocon 2017 are being summarized. Three abstracts presented in the conference were international studies and they have not been reviewed here as the studies were not conducted in India. Case reports and short case series were excluded from the analysis. Data pertaining to stem cell transplant is reviewed elsewhere [1].

Molecular Biology and Laboratory Aspects of Plasma Cell Disorders

The advances in molecular biology have made significant changes on the ways we risk stratify Multiple Myeloma (MM). Focus on risk stratification in MM has been shifting from conventional metaphase cytogenetics to interphase Fluorescent in situ hybridization (iFISH), Gene Expression Profiling (GEP) and whole exome sequencing. There is paucity of data on the cytogenetic profile of MM patients from South East Asian countries including India. A previous study by Kadam et al. reported the distribution of various cytogenetic subgroups in MM patients belonging to Indian ethnicity however data on clinical and biochemical characteristics were not reported [2]. In the abstract number

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PCD-05, Jain et al. retrospectively analyzed the FISH findings on purified CD138 selected bone marrow aspirate cultured plasma cells in 95 MM cases belonging to Indian ethnicity and co-related the results with clinico-biochemical parameters [3]. Cytogenetic abnormalities were detectable in 66% of patients which is comparable (50–90%) to the that reported in literature [4]. Monosomy 13/del(13q) was seen in 40% patients followed by IgH translocations in 32%, gain (1q21) in 26% and TP53 deletion/monosomy 17 in 8% patients. Hyperdiploidy was found in 36% patients. Median age of patients was 55.5 years (range 27–84 years). IgH translocation and TP53 deletion correlated with advanced stage disease ($p < 0.042$), whereas monosomy 13/del(13q) was significantly associated with high plasma cells ($p < 0.043$). At a median follow up of 3 months, patients on cyclophosphamide based therapy showed an overall response rate (ORR) [complete response (CR) + very good partial response (VGPR)] of 86% whereas those on lenalidomide based therapy showed an ORR of 61.5%. The study also revealed some of the important differences in the MM patients of Indian ethnicity as compared to western patients. These included a lower median age at 55.5 years (a decade younger than those from other countries), a lower prevalence of gain 1q21 (26 vs. 40% reported from west); lower prevalence of chromosome 13 aberrations (40 vs. 50% previously reported) while the prevalence and clinical characteristics of IgH translocations (32% in the current study vs. 30% reported from west) and del17p (8% in current study vs. 10% reported from west) appeared similar to other ethnicities [5]. This study is one of the initial studies on the cytogenetic profile of MM patients belonging to Indian ethnicity.

Gene expression profiling (GEP) is a unique tool which helps us to look at the disease biology in a very broad sense in a given myeloma patient. However, data on the impact of gene expression signatures in the era of novel therapies are evolving. The 2 major GEP based classification of MM are the TC Classification system and the UAMS classification. The TC classification was based on expression of D type of cyclins while the UAMS classification detected additional clusters that had additional features in terms of response to therapy [6, 7]. In the abstract number PCD-04 by Behere et al. [8] microarray data (gene expression profiles) for newly diagnosed multiple myeloma patients was obtained from NCBI—Gene Expression Omnibus (specifically the dataset GSE2658) and genes exhibiting highly variable gene expression were selected (standard deviation – 1.34) for further analysis. Statistically significant genes across all classes were selected using SAM (Significance analysis of microarrays) following which a 644 gene classifier was built and validated using PAM (Prediction analysis for microarrays). Survival curves for

expression free survival and overall survival were made for each class using Kaplan–Meier method. Also, survival curves comparing the effect of two therapy regimes named as TT2 and TT3 were made for each class. Using the above mentioned techniques the authors were able to identify six subclasses for newly diagnosed MM based on their GEP. Survival analysis for progression free survival (PFS) and overall survival (OS) done for each of the obtained classes revealed a clear overall OS benefit for groups 1, 2 and 4 while groups 2 and 5 had a favorable PFS. Survival analysis for PFS and OS was repeated for each class taking the two therapy regimes TT2 and TT3 (incorporates bortezomib) into consideration. It was seen that TT3 conferred a significant OS benefit in all classes except for groups 4 and 5 and better PFS in all classes. This data provides us with valuable insight on GEP based risk stratification of MM and further our goals towards practice of precision medicine.

Besides molecular and cytogenetic studies, the immunohistochemistry is frequently used as a surrogate marker of protein expression and prognosis in hematologic malignancies. Immunohistochemical studies also enable to identify possible targets for therapy [9]. The heterogeneous antigen expression of myeloma cells may have impact on clinical outcome in MM. CD 20 expression in MM cells has been reported variably from 15 to 22% depending upon on the cut-off of positive value used [10, 11]. Cyclin D1 positivity is found in up to 32% patients of MM by ISH and up to 25% patients of MM by immunohistochemistry [12, 13]. There is some data to suggest that cyclin D2 expressing CD 20 + MM patients have aggressive disease than cyclin D1 expressing patients and that patients with cyclin D1 expression may be candidates for anti CD 20 directed therapy [9]. A correlation has also been reported between small mature plasma cells, CD20 and t(11;14) in patients with MM [14]. Clinical trials show that anti-CD20 therapy with rituximab elicits a partial response in approximately 10% of CD20+ patients with MM. In addition, there is preliminary evidence of disease stabilization in 50–57% of CD20+ patients for a period of 10–27 months. In the abstract number PCD-13 by Mallik et al. CD 20 and cyclin D1 expression was retrospectively studied in 62 trephine biopsy specimens of MM and was correlated with outcome. CD 20 expression was found in 14.7% patients and cyclin D1 expression was found in 21.6% patients which is nearly equivalent to the data previously reported [15]. In their dataset 75% of patients with CD20 positivity or cyclin D1 positivity showed complete or a better response; while only 58.3% of the CD20 negative and 57.8% of the cyclin D1 negative myeloma cases showed complete or a better response suggesting a favourable prognostic impact of CD20 and cyclin D1 expression in MM. Previously Cook et al. have reported

significantly superior survival in cyclin D1 positive MM as compared to cyclin D1 negative patients (73 vs. 27%) and a similar trend was shown by Mallik et al. [16].

Clinical Characteristics

In abstract PCD-04 that reported clinical profile of 45 patients of MM patients presenting to tertiary care center of north eastern Assam, the mean age was reported to be 57.7 years (SD 10.29) which is again around 10 years lower than the average age reported in western literature. While the frequency of other clinical features like bony pains, fatigue and anemia was similar to the previously reported data, the authors have reported a very high frequency of spinal cord compression (30%) and paraplegia (32%) as compared to 5–15% reported in literature [17]. These data are concerning and reflect the late presentation of MM cases to the health care facility with advanced MM related complications in India.

Light Chain MM constitutes up to 15% of all MM patients and is known to be associated with anemia, higher ISS scores, proclivity to renal failure, elevated LDH levels, higher frequency of extramedullary plasmacytomas and poorer overall survival [18]. Singh et al. in their abstract number O06 reported their experience of Light Chain MM in the retrospective analysis of 104 consecutive patients of newly diagnosed MM who presented to their center in previous 3 years [19]. LCM was seen in 24 patients (23%) patients with almost equal distribution of Kappa and lambda subtypes (54 and 45% respectively). On univariate analysis, LCM patients showed statistically significant correlation with younger age group, lesser degree of anaemia and higher SFLC ratios in comparison to the IgG and IgA subtypes. No difference was found in terms of serum LDH, renal impairment, presence of bony or extramedullary lesions, ISS-scores, pre-transplant chemosensitivity and PFS in patients of light chain MM as compared to other MM subtypes. It seems likely that using standardized proteasome inhibitor based treatment, the negative prognostic impact of light chain MM can be circumvented.

Treatment of Plasma Cell Dyscrasias

One of the earliest experience of the use of Daratumumab in the Indian population was presented by Ahmed et al. [20]. Daratumumab was used as combination therapy in 7 patients of relapsed or RRMM. The patients had received a median of 2 lines of therapy and 4 out of 7 patients were refractory to both immunomodulatory agents and proteasome inhibitor. The authors found an ORR of 42.7%.

Hematologic toxicity was most common (neutropenia and thrombocytopenia), 2 patients had grade 3–4 thrombocytopenia and 2 patients had grade 3–4 neutropenia and there were 2 deaths due to gram negative sepsis and H1N1 respectively. While the efficacy of this molecule in RRMM is well established, further data is required to elucidate the toxicity profile of this molecule in Indian patients given the limited data available from India.

Conclusion

The above findings highlight the rapidly evolving science of managing plasma cell dyscrasias in the country and abroad. Our future goals should aim at encouraging multi-centric collaborative research across the country so that robust clinical data can be generated to improvise upon the practice of dealing with these disorders amidst the challenges unique to developing countries.

Compliance with Ethical Standards

Conflict of interest We have no financial relationships to disclose.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

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