Indian J Hematol Blood Transfus (Oct-Dec 2021) 37(4):679–683
https://doi.org/10.1007/s12288-021-01410-3

SHORT COMMUNICATION

Multiple Myeloma in Young Adults: A Single Centre Real World Experience

Venkateswar Rao Pydi[1] · Stalin Chowdary Bala[1] · Siva Prasad Kuruva[1] · Rachana Chennamaneni[1] · Meher Lakshmi Konatam[1] · Sadashivudu Gundeti[1]

Received: 31 December 2019 / Accepted: 9 February 2021 / Published online: 27 February 2021

Abstracts Multiple Myeloma accounts for 1% of all cancers. In India myeloma accounts for 1.23% of all cancers. The median age at diagnosis varies from 65 to 70 and only a small proportion of MMs are diagnosed at younger age, before 40 (approximately 2%). The present study is designed to analyse the clinical, haematological profile and outcomes in young adults with multiple myeloma. Data of all patients with age $\leq$ 40 years, diagnosed with multiple myeloma from 2013 to 2018 was analysed. A total of 258 patients were diagnosed with multiple myeloma between 2013 and 2018, of which 22 (8.5%) were aged $\leq$ 40 years. The median age was 33.5 years(range,18–40). Male to female ratio was 1.75:1. Bone pain (59%) and fatigue (45.4%) were the most common symptoms at presentation. Majority of patients were ISS stage 3(63.6%). Cytogenetic data was available only in seven patients and IgH translocation and del 13q were the most common abnormalities, seen in four and three patients respectively. Of 22 patients, 17 patients had at least one response evaluation and were evaluated for outcomes. Eleven patients (64.7%) had responses greater than VGPR. Six (41.6%) patients underwent Auto HSCT. Four patients received second line therapy and only two received further lines of therapy. At a median follow up of 18 months, 2-year EFS was 76.5% and 2-year OS was 94.1%. Patients younger than 40 years, constitute higher proportion of patients in Indian sub-continent. Renal failure was more common in young myeloma patients. Light chain myeloma was more common in young adults. Most patients were ISS stage 3 at presentation and survival seems to be better in young adults when compared to elderly patients.

Keywords Multiple myeloma · Young · Renal failure · Hypercalcemia · Survival

Introduction

Multiple myeloma, characterized by clonal plasma cell proliferation and end organ damage like anemia, hypercalcemia, bone lytic lesions and renal failure accounts for 10% of all hematological malignancies [1]. The median age diagnosis of myeloma varies from 60 to 75 years and it occurs a decade earlier in India. Diagnosis of myeloma below 40 years is rare and the published literature on outcomes in young myeloma patients from Indian subcontinent is scarce [2]. Among published studies, mixed results were seen in outcomes compared to elderly counterparts, some showing better outcomes and some showing no difference in outcomes compared to elderly patients [3–7]. Lack of comorbidities and higher proportion of young patients being fit for stem cell transplantation has been considered reasons for better performance in this subset of patients [8]. The present study was designed to analyse clinico-hematological profile, treatment responses and survival in young adults with multiple myeloma.

Materials and Methods

Between 2013 and 2018, patients with a proven diagnosis of MM and aged 40 years or younger were analyzed. The study protocol was reviewed and approved by the Institutional Review Board. Analysed parameters included age at diagnosis, gender, paraprotein isotype, International

✉ Stalin Chowdary Bala
stalinchowdarybala@gmail.com

[1] Department of Medical Oncology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad 500082, India

Scoring System (ISS) for MM, Revised ISS, serum haemoglobin, serum calcium, creatinine, albumin and beta-2 microglobulin, lactate dehydrogenase (LDH) level and radiological evidence of lytic lesion. Presence of cytogenetic abnormalities was determined by means of fluorescence in situ hybridization (FISH): del(17/17p), t(4;14), t(11;14), del(13q) and conventional karyotyping. Data of front-line anti-MM treatment received, and therapeutic responses were noted down.

Regimens used were VRd (Bortezomib, Lenalidomide, Dexamethasone), VTd (Bortezomib, Thalidomide Dexamethasone), CyBord (Cyclophosphamide, Bortezomib and Dexamethasone), Vd and Rd. Patients with renal dysfunction received VTd or CyBord regimen. Front line Autologous stem cell transplantation (ASCT) was offered to all patients and was performed when consent was provided and post ASCT patients received either lenalidomide or bortezomib maintenance till progression.

Treatment outcomes were classified as complete response (CR), very good partial response (VGPR), partial response (PR) and stable disease and progressive disease. Overall response rate (ORR), that is, the proportion of all responses > PR, was calculated. Event Free Survival (EFS) was defined as time in months between diagnosis and any event (progression, relapse or death). Overall Survival (OS) was defined as the time in months from MM diagnosis to death from any cause. Kaplan Meir curves were used for survival estimation and log rank test was used for within group comparison. All the statistical analyses were performed using SPSS, version 25.0 (IBM corporation, NY, USA).

Results

A total of 258 patients were diagnosed with multiple myeloma between 2013 and 2018, of which 22 (8.5%) were aged ≤ 40 years. The median age at presentation of whole population was 56 years (range, 18–84) and median age of patients younger than forty years was 33.5(range-18–40). There was a male preponderance with a male to female ratio was 1.75:1. Bone pain (59%) and fatigue (45.4%) were the most common symptoms at presentation. Twenty patients(90.9%) had ECOG PS ≤ 2 at presentation.

The median hemoglobin, creatinine, creatinine clearance and calcium were 9.4 g/dL(range, 5.4–14.4), 1.85 mg/dL(range, 0.6–19), 52.5 ml/min(range, 4–119), 9.2 mg/dL(range, 8.1–13.5) respectively. CRAB features, Immunofixation and ISS stage comparison of young myeloma patients and total patients was shown in Table 1. The median albumin and beta 2 microglobulin were 4.1 mg/dL(range, 2.3–3.5) and 5.1 mg/ml(range, 1.8–20). Elevated beta 2 microglobulin(> 5.5 mg/ml) and LDH(> 440 U/L) were seen in 50% and 53% patients respectively.

Cytogenetic data was available only in seven patients of which three patients had normal karyotype. IgH translocation and del 13q were the most common abnormalities, seen in four and three patients respectively. Two patients had t(11;14), one each had t(4;14) and t(14;16) translocation. One patient had 17p deletion. R ISS staging details available in 11 patients showed Stage I, Stage II and Stage III in one patient(9.1%), three patients(27.3%) and seven patients(63.6%) respectively.

Treatment Response and Survival

Of 22 patients, 17 patients had at least one response evaluation and were analysed for outcomes. The largest proportion of patients (12/17, 70%) received triplet therapy, most often PI combined with IMIDs. Front line Autologous stem cell transplantation (ASCT) was offered to all patients and was performed in seven patients (41.6%). VRd was the most common regimen with 100% CR rate.

The overall response rates with various regimens were VRd(CR 5/5), VTd(CR 2/3, PR 1/3), CyBord(VGPR 1/4, PR, 1/4 and SD 2/4), Rd(CR 1/1), Vd(CR 2/4, SD 2/4). Among the patients who received combination chemotherapy and underwent ASCT the responses were CR(4/7), VGPR(1/7), PR(1/7) and SD(1/7). The median dose of induction cycles before ASCT were 4 cycles. At the time of data analysis, eleven patients were on maintenance therapy with either bortezomib, lenalidomide or thalidomide. Three patients were lost to follow up and two patients had died. Four patients received second line therapy and only two patients received further lines of therapy.

Out of 9 patients who had serum creatinine > 2 mg/dL at presentation. Renal biopsy was done in 5 patients of which two patients showed acute tubular necrosis and three patients had cast nephropathy. Hemodialysis was used initially for 5 patients. Of nine patients, five patients (55.5%) had normalisation of creatinine after therapy. Out of remaining four patients two patients had partial renal response and remaining two patients had no response. Two patients were dialysis dependent at the time of analysis.

At a median follow up of 18 months, two-year EFS was 78.5% and 2-year OS was 94.1%. None of the analysed variables like male sex, PS > 2, Hemoglobin < 10 g/dL, renal failure, elevated LDH, hypercalcemia, Plasma cells > 60%, FLC > 100, ISS stage 3, triplet therapy vs doublet therapy, IgG vs Non IgG, ASCT vs non ASCT significantly predicted EFS on univariate analysis(p = 0.36, 0.9, 0.9, 0.8, 0.4, 0.2, 0.2, 0.6, 0.8, 0.29, 0.8 and 0.49 respectively). Of 7 patients who underwent ASCT, one patient succumbed to progressive disease after

Table 1 Clinical characteristics of young adults with multiple myeloma

Characteristic	Whole group (n = 22)	Total population (n = 258)
CRAB Criteria		
Haemoglobin < 10 g/dL	15(68.2%)	162(62.7%)
Creatinine > 2 mg/dL	11(50%)	94(36.4%)
Calcium > 11 mg/dL	2(9.1%)	68(26%)
Bony lesions	13(59%)	195(75.5%)
Immunofixation		
IgG kappa	7(31.8%)	123(54.6%)
IgG lambda	4(18.2%)	
IgA kappa	1(4.5%)	26(11.5%)
Kappa light chain	5(22.7%)	28(12.4%)
Lambda light chain	4(18.2%)	46(20.4%)
ISS stage		
Stage 1	4(18.2%)	43(17.4%)
Stage 2	7(31.8%)	81(32.9%)
Stage 3	11(50%)	122(49.5%)

45 months of disease onset, one patient had relapse after 26 months and received second line therapy, 5 patients are on maintenance therapy.

Discussion

Multiple Myeloma, usually a disease of elderly is rare in adolescent and young adults. The published literature on outcomes in young myeloma patients is scant. The present study was planned to analyze outcomes in young myeloma patients and to best of our knowledge, this is the second series from India other than study by Yanamandra et al. [9].

The incidence of MM in young adults in the current study was 8.5%, which was higher compared to western studies[2, 3, 6] but similar to other Indian study by Yanamandra et al. [9]. MM presents a decade earlier in Indian subcontinent when compared to the west [9], the probable reason could be the higher proportion of young people in the population pyramid of Indian subcontinent.

The published literature showed that there are no differences in clinical and laboratory characteristics of young patients when compared to general myeloma population. In the present study renal failure at presentation was seen in 50% of young patients which was higher compared to studies by Ludwig et al. [3] and Shin et al. [7], the probable reason being majority of our patients referred from our nephrology clinic. Hypercalcemia at diagnosis was seen in 9% of our patients, slightly lower than published studies. Anemia at presentation was seen in 68% of patients compared to 37% and 31% by Ludwig et al. [3] and Jurczyszyn et al. [8], probably due to late presentation and higher incidence of renal failure in our patients also contributing to anemia. Bone disease at presentation of 59% was similar to other Indian study by Yanamandra et al. [9] but less compared to western studies, possible explanation being more use of plain radiographs in the present study for skeletal survey.

In the present study, Immunofixation showed IgG M protein as the most common subtype, followed by light chain disease. Studies by Blade et al. [10] and Shin et al. [7] showed higher light chain disease in younger patients similar to that seen in present study. Majority of patients in present study had ISS-3 at presentation similar to other Indian study by Yanamandra et al. [9], this could be due to late presentation and referral to myeloma clinic. Comparison of clinical characteristics with other studies was shown in Table 2.

Complete response was the most common response seen in the present study and all patients receiving VRd had CR at evaluation. This is almost similar to study by Jurczyszyn et al. Though ASCT was offered to all patients, only a small percentage underwent transplantation due to financial constraints. 41% of our patients underwent transplant which was higher compared to study by Yanamandra et al. [9] (22.5%). The 2 year EFS and OS OF 78.5% and 94.1% in the present study was higher in younger patients compared to overall multiple myeloma population of 41.8% and 76.6% respectively. Studies by Ludwig et al. [3] and Jurczyszyn et al. [8] also showed superior outcomes in young patients compared to elderly. In study by Jurczyszyn et al. [8] 5 year and 10-year OS was higher for younger patients(83% and 56% respectively) compared to elderly people (67%and 39%) but studies by Cheema et al. [6] did not show any survival difference between young and older patients. In the present study, none of the variables analyzed predicted for EFS. This could be probably due to less number of patients. Large collaborative studies may be

Table 2 Comparison of clinical characteristics of young adults with multiple myeloma across studies

Characteristic	Present study N = 22	Yanamandra et al. [9] N = 40	Ludwig et al. (age < 50) [3] N = 1689	Cheema et al N = 38 [6]	Jurczyszyn et al N = 173 [4]	Shin et al N = 32 [7]
< 40 years	8.5%	9.6%	2.9%	6.6%	16%	–
Median age	33.5(25–40)	38(18–39)	36(20–49)	37.2(29.3–40.1)	37(21–40)	37(17–40)
Male sex	63.6%	65%	67%	61%	60%	59%
ISS stage						
Stage 1	18.2%	12.5%	39%	48%	47%	32%
Stage 2	31.8%	17.5%	35%	–	33%	48%
Stage 3	50%	70%	27%	–	20%	19%
M protein subtype						
Light chain	40.9%	11%	13%	21%	14%	30%
IgG	50%	76%	60%	53%	69%	47%
IgA	4.5%	11%	21%	18%	17%	17%
Haemoglobin < 10 mg/dL	68.2%	52.5%	37%	–	31%	29%
Calcium > 11 mg/dL	9%	24.3%	33%[a]	23%	16%	28%[a]
Bone disease	59%	59.2%	79%	76%	82%	87%
Creatinine > 2 mg/dL	50%	30%	15%	25%	25%	13%
ASCT	41%	22.5%	5.7–78.7%[b]	100%[c]	47.9%	62%

[a]Proportion of patients with Calcium < 10 mg/dL were reported in these studies

[b]1981–87—5.7%, 1988–92—16.1%, 1993–98—59.4%, 1999–2002—78.7%

[c]ASCT was inclusion criteria in this study

needed to analyse factors predicting survival in younger patients.

The present study has several limitations. First, this study is a retrospective and it has all the limitations associated with it. Second, the study is based on small number of patients and results should be interpreted with caution. Being retrospective analysis, data regarding toxicity of therapy and cause of death were not available.

Conclusion

Patients younger than 40 years constitute higher proportion of patients in Indian sub-continent. Renal failure was more common in young myeloma patients. Light chain myeloma was more common in young adults. Most patients were ISS stage 3 at presentation. Also, survival seems to be better in young adults when compared to elderly patients which needs to be proved with longer follow up.

Acknowledgements Department of Pathology, Nizam's institute of Medical Sciences

Funding This research did not receive any specific grant from funding agencies in public, commercial, or not-for- profit sectors.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME (2003) Review of 1027 patients with newly diagnosed multiple myeloma. Mayo ClinProc 78(1):21–33
2. Bladé J, Kyle RA (1998) Multiple myeloma in young patients: clinical presentation and treatment approach. Leuk Lymphoma 30(5–6):493–501
3. Ludwig H, Durie BG, Bolejack V, Turesson I, Kyle RA, Blade J, Fonseca R, Dimopoulos M, Shimizu K, San Miguel J, Westin J (2008) Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10, 549 patients from the International Myeloma Working Group. Blood 111(8):4039–4047
4. Jurczyszyn A, Nahi H, Avivi I, Gozzetti A, Niesvizky R, Yadlapati S, Jayabalan DS, Robak P, Pika T, Andersen KT, Rasche L (2016) Characteristics and outcomes of patients with multiple myeloma aged 21–40 years versus 41–60 years: a multi-institutional case-control study. Br J Haematol 175(5):884–891
5. Corso A, Klersy C, Lazzarino M, Bernasconi C (1998) Multiple myeloma in younger patients: the role of age as prognostic factor. Ann Hematol 76(2):67–72

6. Cheema PK, Zadeh S, Kukreti V, Reece D, Chen C, Trudel S, Mikhael J (2009) Age 40 years and under does not confer superior prognosis in patients with multiple myeloma undergoing upfront autologous stem cell transmplant. Biol Blood Marrow Transpl 15(6):686–693
7. Shin J, Koh Y, Youk J, Kim M, Kim BS, Choi CW, Sung HJ, Park Y, Yoon SS, Kim I (2017) Clinicopathological characteristics of extremely young Korean multiple myeloma patients: therapeutic implications. Korean J Intern Med 32(4):722
8. Jurczyszyn A, Davila J, Kortüm KM, Jayabalan DS, Vij R, Fiala M, Milunovic V, Chim CS, Wiśniewska-Piąty K, Waszczuk-Gajda A, Crusoe E (2019) Multiple myeloma in patients up to 30 years of age: a multicenter retrospective study of 52 cases. Leuk Lymphoma 60(2):471–476
9. Yanamandra U, Saini N, Chauhan P, Sharma T, Khadwal A, Prakash G, Varma N, Lad D, Varma S, Malhotra P (2018) AYA-myeloma: real-world, single-center experience over last 5 years. J Adolesc Young Adult Oncol 7(1):120–124
10. Bladé J, Kyle RA, Greipp PR (1996) Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. Br J Haematol 93(2):345–351